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(54) Title: PROCESS FOR PREPARATION OF CLOPIDOGREL, ITS SALTS AND PHARMACEUTICAL COMPOSITIONS

(57) Abstract: The invention discloses an improved process for racemization of methyl (R)(-) alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate , a stereoisomer formed in the synthesis of clopidogrel i.e. methyl (S)-(+)-alpha (2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate or its salts. The invention is also for an improved process for production of clopidogrel or its pharmaceutically acceptable salts. The invention further discloses novel clopidogrel salts and pharmaceutical compositions comprising them.

WO 2004/074215 A1

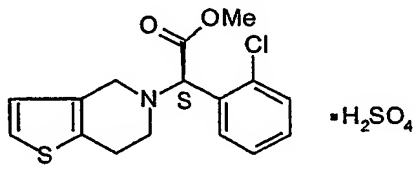
PROCESS FOR PREPARATION OF CLOPIDOGREL, ITS SALTS AND PHARMACEUTICAL COMPOSITIONS

FIELD OF THE INVENTION

The invention relates to an improved and cost effective process for preparation of clopidogrel and its salts including clopidogrel bisulphate, a biologically active thiophene, preparation of pharmaceutically acceptable salts of clopidogrel and pharmaceutical compositions containing them. The invention also relates to novel salts of clopidogrel, their preparation and pharmaceutical compositions comprising them.

DESCRIPTION OF THE RELATED ART

Clopidogrel bisulfate (I) *i.e.*, methyl (S)-(+)-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate sulphate, is an ADP (Adenosine Di-Phosphate) receptor antagonist that is indicated for the reduction of atherosclerotic events including myocardial infarction, ischaemic stroke and vascular death in patients with atherosclerosis manifested by recent stroke, myocardial infarction or established peripheral vascular disease (Blair Jarvis and Kerryn Simpson, Drugs 2000, Aug; 60(2): 347-377).

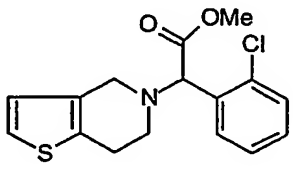


(I)

Atherothrombosis can give rise to unstable angina, myocardial infarction or stroke in susceptible individuals. Platelets, which do not interact with the endothelium of normal vessels, play a central role in atherothrombosis by adhering to exposed sub-endothelial structures in damaged vessels.

Platelets may be activated by several substances. Among these, ADP plays an important role. ADP is present in high concentrations in the dense granules within platelets and can initiate and reinforce aggregation after secretion of these granules (George JN. Platelets. Lancet 2000 Apr. 29: 355: 1531-9). Clopidogrel bisulfate is an antiplatelet agent that selectively and irreversibly blocks ADP-induced platelet aggregation. After activation by cytochrome P450 (CYP)-mediated hepatic metabolism, clopidogrel bisulfate is a selective and irreversible inhibitor of ADP-induced platelet aggregation (Blair Jarvis and Kerryn Simpson, Drugs 2000, Aug; 60(2): 347-377).

In literature, it is known that methyl-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate of formula (II) and its salts can be used in the treatment of platelet aggregation inhibitory and anti-thrombotic effect. The process for preparing methyl-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate and its salts are described in WO 98/51689.

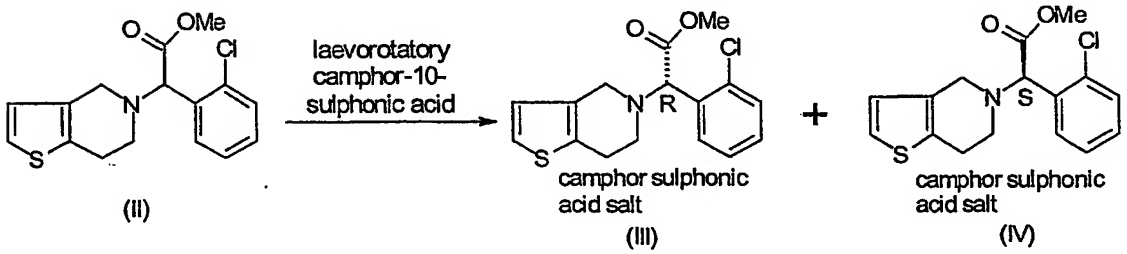


(II)

According to US 4,847,265, it was found that the biological activity resides only with (+)-stereoisomer *i.e.*, methyl (S)-(+)-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate sulphate (I) also known as clopidogrel bi-sulphate.

Also, US 4,847,265 describes the process to obtain clopidogrel bisulphate (I) *i.e.*, methyl(S)-(+)-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate sulphate, wherein methyl-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate (II) is resolved by laevorotatory camphor-10-sulfonic acid to give methyl(R)-(-)-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate camphor sulfonic acid salt (III), which remains in the mother liquor and can be converted in to methyl (R)-(-)-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate (XII) by known method, where as methyl(S)-(+)-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate camphor sulfonic acid salt (IV) separates out as solid as shown in Scheme 1.

Scheme 1



(II) (III) (IV)

Further, in order to obtain clopidogrel bisulfate (I), the methyl (S)-(+)-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate camphor

sulfonic acid salt (IV) is converted into (+)- stereo isomer of (II) *i.e.*, methyl (S)-(+)-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate by using aqueous sodium bicarbonate in dichloromethane, which is further reacted with H_2SO_4 in acetone to give desired product, clopidogrel bisulfate(I). However, the undesired isomer *i.e.*, methyl (R)-(-)-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate camphor sulfonic acid salt (III), which remains in mother liquor is unused and hence is practically considered as waste. Also, it should be noted that a part of useful salt *i.e.*, methyl (S)-(+)-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate camphor sulfonic acid salt (IV), which remains dissolved in mother liquor is also not recovered. Hence, the quantities of (III) and (IV) from mother liquor are wasted.

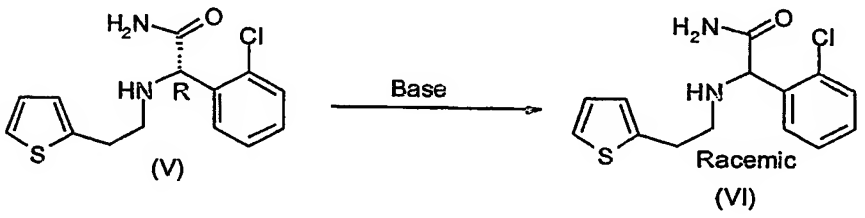
If the undesired R-isomer (III) is not used then, the resolution step being the extreme last step, all the reagents, solvents, drying agents, purification agents, utilities, manpower from the first step of the synthesis till the resolution step which are used up in the formation of discarded R-isomer (III) are wasted.

Considering the high demand of the potential drug, there is a need for a process, which uses the undesired isomer *i.e.*, methyl (R)-(-)-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate camphor sulfonic acid salt (III) in an intelligent way. Also, the recovery of useful salt *i.e.*, methyl (S)-(+)-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-

acetate camphor sulfonic acid salt from mother liquor is necessary for the process economy.

As mentioned in Scheme 2, WO 00/27840 (Sanofi - Synthelabo) describes the racemization of undesired intermediate amide (V) *i.e.*, (-)-[2-(2-thienyl)ethylamino] (2-chlorophenyl)acetamide. The racemization process converts undesired R-isomer of amide (V) into racemic amide (VI) *i.e.*, [2-(2-thienyl)ethylamino] (2-chlorophenyl)acetamide using base.

Scheme 2



Further racemized amide (VI) is converted to clopidogrel bisulfate (I) as shown in Scheme 3.

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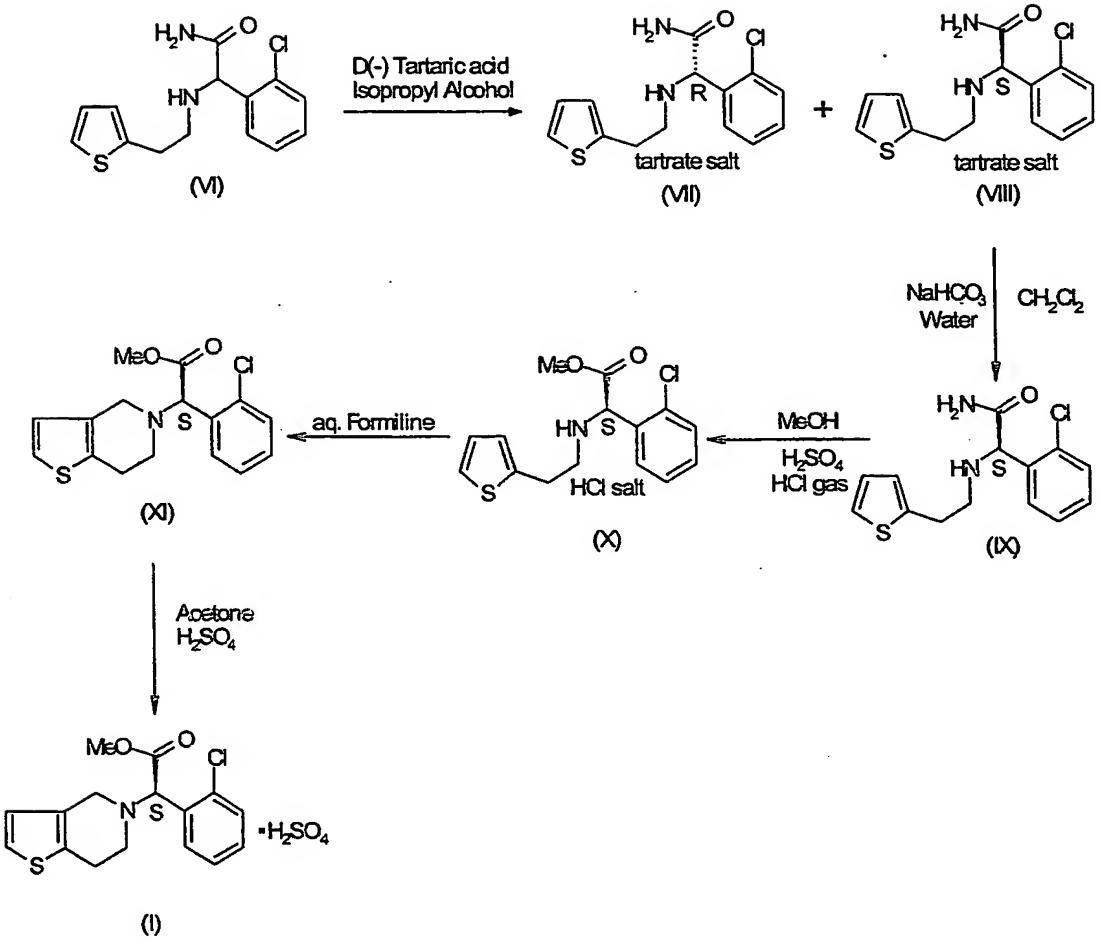
Scheme - 3



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The drawback of the above synthetic route is that racemized amide (VI) further needs to be converted into clopidogrel bisulfate(I) by a number of reaction steps as shown in Scheme 3. Thus, it requires more number of reaction steps for recycling racemic amide (VI), in order to get the final product *i.e.*, clopidogrel bisulfate (I). Also, it requires more (a) time, (b) reagents, (c) solvents, (d) purifying agents, (e) manpower, (f) utility, which makes this recycling of undesired stereoisomer to get clopidogrel bisulfate a costlier process.

Also, WO 02/059128 describes the process for the racemization of undesired R- isomer *i.e.*, compound (V) to intermediate amide (VI) as well as undesired

R-isomer of compound (II) in the presence of base. The main drawback of this process lies in the use of base such as potassium tert-butoxide, sodium hydride which are hazardous and costly base.

It needs to be appreciated that there is a need for a racemization process for the preparation of clopidogrel bisulfate (I), which converts undesired R-isomer into racemic form. Also it should require minimum (a) reaction steps, (b) time, (c) reagents, (d) solvents, (e) purifying agents, (f) manpower and (g) utility and also devoid of hazardous reagents to make the process cost-effective and commercially viable.

In US 4,847,265, the reaction-step for the conversion of racemic clopidogrel base to the camphor sulphonate salt of methyl (S)-(+)-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate requires a reaction time period of 72 hrs and is also accompanied by intermittent work-up for volume reduction. This implies increase in utilities and manpower to complete the production cycle, rendering the process commercially expensive. Thus, there is need to reduce the reaction time of the said reaction, while simultaneously reducing the work-up to make the process convenient and economically more viable.

In US 4,847,265, it is acknowledged that various salts namely acetate, benzoate, fumarate, maleate, citrate, tartrate, gentisate, mesylate, benzene sulfonate, lauryl sulfonate, dobesilate, tosylate and hydrochloride of clopidogrel are hygroscopic and thus makes them difficult to handle on industrial scale. Thus, there is difficulty in their purification, isolation and storage. Furthermore, these salts are amorphous. For preparation of pharmaceutical composition the compound *i.e.*, active pharmaceutical ingredient (API) is preferred in the form of crystalline nature. The pharmaceutical usage always demands pure compounds, as it goes for human consumption. However, the impure compounds, which are the results of purification difficulty, cannot lead to a drug in the market. Hence, there is a need for a process of their production, which can be handled on an industrial scale and can generate crystalline compound.

OBJECTS OF THE INVENTION

It is an object of the invention to recycle the undesired R-isomer namely methyl (R)-(-)-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate (XII), in the synthesis of clopidogrel and its salts, which is practically considered as waste, and make the process more cost effective and commercially viable.

Another object of the invention is to provide an improved process for racemization of the said R-isomer for recycling to the process for synthesis of clopidogrel

Yet another object of the invention is to provide an improved commercially viable and cost effective racemization process towards the synthesis of the clopidogrel or its salts, which requires minimum (a) reaction steps, (b) time, (c) reagents, (d) solvents, (e) purifying agents (f) manpower and (g) utility and also avoids hazardous reagents.

A further object of the invention is to reduce the time required for the preparation of the reaction intermediates.

A still further object of the invention is to provide a cost effective method of preparation of clopidogrel and its salts, namely clopidogrel mesylate,

clopidogrel hydroiodide and clopidogrel perchlorate, and the other pharmaceutically acceptable salts mentioned herein.

Still another object of the invention is to provide the industrially suitable procedure to synthesize the pharmaceutically acceptable salts of clopidogrel.

Another object of the invention is to provide novel clopidogrel salts.

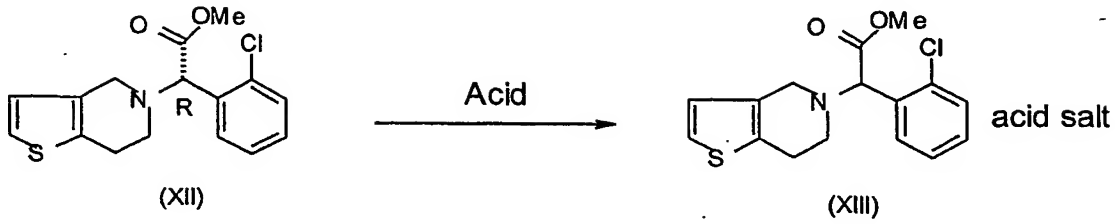
A further object of the invention is to provide pharmaceutical composition with clopidogrel salts.

SUMMARY OF THE INVENTION

The present invention accordingly provides a process for the racemization of methyl(R)-(-)-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate (XII) to prepare methyl-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate (II) and pharmaceutically acceptable salts thereof such as clopidogrel bisulfate (I),

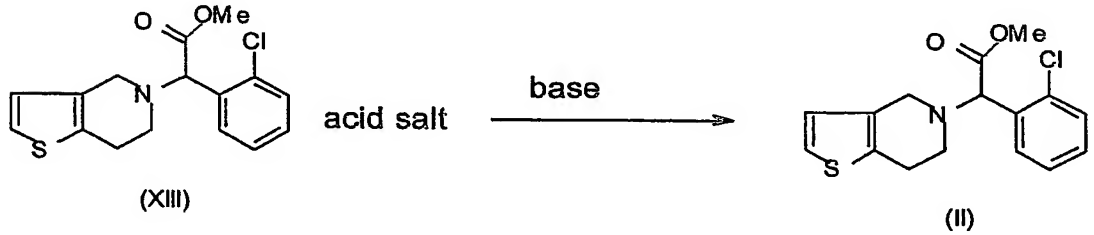
which comprises the steps of

(a) reacting methyl (R)-(-)-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate (XII) with acid in suitable solvent at a temperature range of 60-100° C to produce the racemic methyl -alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate acid salt (XIII).



(XII) (XIII)

(b) reacting methyl-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c] pyridine-5(4H)-acetate acid salt (XIII) with base to produce the racemic methyl-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate (II)



(XIII) (II)

(c) converting methyl-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c] pyridine-5(4H)-acetate(II) to its pharmaceutically acceptable salts thereof in a manner known per se.

The acid used in the step (a) is selected from the group comprising of HCl, H_2SO_4, CH_3COOH, H_3PO_4. The preferred acid is selected from HCl, H_2SO_4. The most preferred acid is HCl.

The solvent used in the step (a) is selected form the group comprising of methanol, ethanol, isopropyl alcohol, n-butanol and tert-butanol. The preferred solvent is isopropyl alcohol.

The base used in the step (b) is selected from the group comprising of sodium hydroxide, potassium hydroxide, sodium ethoxide, liquor ammonia, triethyl amine, diethyl amine and monomethyl amine.

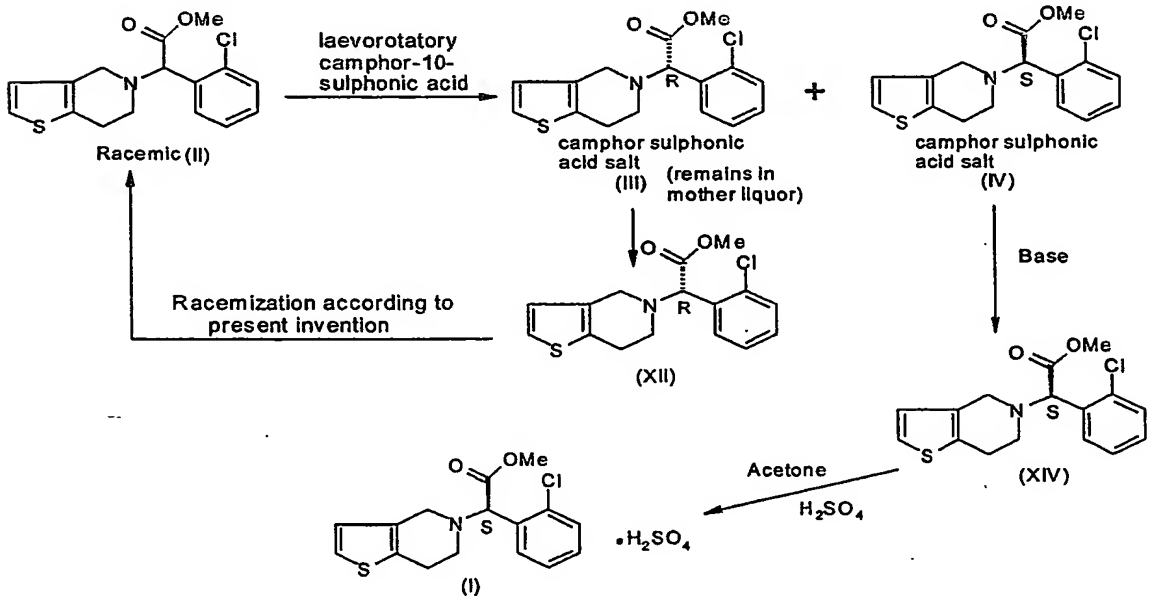
The preferred base is liquor ammonia.

The reaction step (a) is carried out for 30 minutes to 4 hrs.

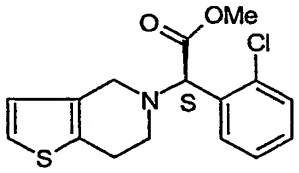
The reaction step (b) is carried out for 15 minutes to 45 minutes.

According to the present invention, undesired R-isomer (XII) is racemized to methyl-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate (II), which is further converted to methyl-(S)-(+)-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate sulphate (I) according to a literature process (US 4,847,265) as given in Scheme -4.

Scheme 4



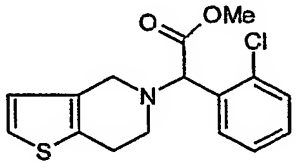
The invention also provides an improved process for the preparation of methyl (S)-(+)-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate (XIV) i.e. clopidfogrel or its pharmaceutically acceptable salt,



(XIV)

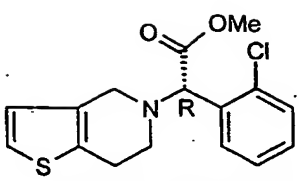
which comprises the steps of:

(a) resolving methyl-alpha-(2-chlorophenyl)-6,7-dihydro- thieno [3,2- c]pyridine-5(4H)-acetate (II)

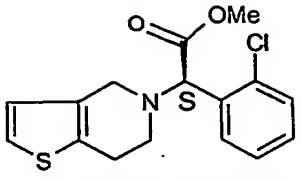


(II)

with laevorotatory camphor-10-sulfonic acid to give methyl (R)-(-) alpha- (2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-4(4H)-acetate camphor sulfonic acid salt (III) and methyl (S)-(+)alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-4(4H)-acetate camphor sulfonic acid salt(IV)



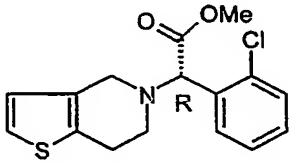
.camphor sulphonate
(III)



.camphor sulphonate
(IV)

(b) separating the two stereoisomers (III) and (IV)

(c) converting the (-) stereoisomer (III) into methyl (R)-(-)alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-4(4H)-acetate (XII)

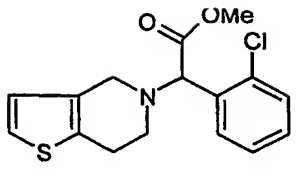


(XII)

by using liquor ammonia in methylene chloride ;

(d)converting (+) sterioisomer (IV) above to methyl (S)-(+)alpha- (2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-4(4H)-acetate (XIV) by using aqueous sodium bicarbonate in dichloromethane ;

(e) racemization of methyl (R)-(-)-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate (XII) by reacting methyl (R)-(-)-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2- c]pyridine-5(4H)-acetate (XII) with an acid in a solvent at a temperature range of 60-100° C to produce the racemic methyl -alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)- acetate acid salt (XIII)



acid salt

(XIII)

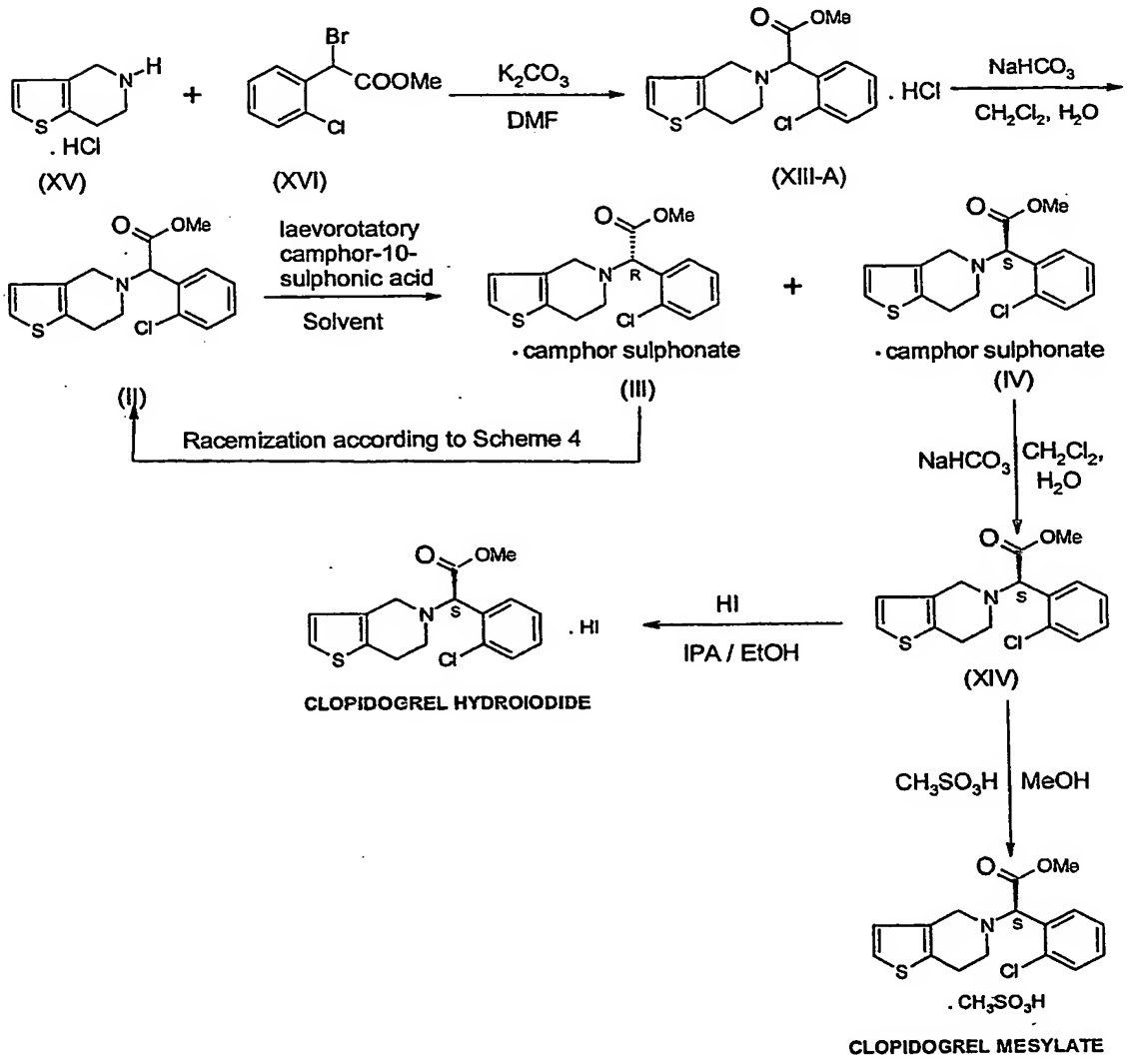
(f) reacting methyl-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c] pyridine-5(4H)-acetate acid salt (XIII) with base to produce the racemic methyl-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate (II) for reuse in step (a).

The present invention further provides novel method of preparation of clopidogrel salts as shown in Scheme - 5, below, which comprises the steps of

(a) condensation reaction between 4,5,6,7-tetrahydrothienopyridine hydrochloride (XV) and methyl –alpha-bromo-2-chlorophenyl acetate (XVI) to give racemic methyl-alpha-(2-chlorophenyl)-6,7-dihydrothieno [3,2-c]pyridine-5(4H)-acetate hydrochloride (XIII-A), which is further treated with a base to obtain racemic methyl-

alpha-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-acetate(II) according to a literature procedure (US 4,529,596).

Scheme 5



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b) dissolving the racemic methyl-alpha-(2-chlorophenyl)-6,7 dihydrothieno[3,2-c]pyridine-5(4H)-acetate (II) in a suitable solvent followed by addition of a chiral reagent like laevorotatory camphor-10-sulphonic acid, wherein the racemic methyl-alpha-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-acetate (II) is resolved to give the camphor sulphonate salt of methyl (S)-(+)-alpha-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-acetate (IV) as a solid, while the camphor sulphonate salt of methyl (R)-(-)-alpha-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5 (4H)-acetate (III) remains in the mother liquor,

c) the camphor sulphonate salt of methyl (R)-(-)-alpha-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-acetate (III) in the mother liquor is further racemized according to Scheme 4 to give racemic methyl-alpha-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-acetate (II).

d) treating the precipitated camphor sulphonate salt of methyl (S)-(+)-alpha-(2-chlorophenyl)-6,7-dihydrothieno[3,2- c] pyridine-5(4H)-acetate (IV) [obtained in step (b) above] with a base to give methyl (S)-(+)-alpha-(2-chlorophenyl)-6,7-dihydrothieno [3,2-c]pyridine-5(4H)-acetate (XIV) in a manner known per se (US 4,847,265) and

e) converting methyl (S)-(+)-alpha-(2-chlorophenyl)-6,7-dihydrothieno [3,2-c]pyridine-5(4H)-acetate (XIV) into its pharmaceutically acceptable salts

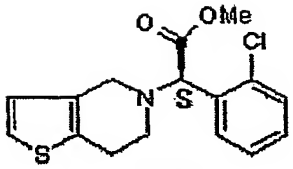
The solvent used for the resolution in step (b) is alkoxy substituted acyclic ethers.

Alkoxy substituted acyclic ether is R-O-R'-O-R'-O-R , wherein, R' = - CH_2 - CH_2 -, R is C_1 - C_3 alkyl, preferably R is methyl.

The preferred alkoxy substituted acyclic ether used as solvent is CH_3-O-CH_2-CH_2-O-CH_2-CH_2-O-CH_3 *i.e.*, bis(2-methoxyethyl)ether (diglyme).

The time required for step (b) is 48 hrs. The reduction of reaction time compared to prior art processes (US 4,847,265), wherein the reaction time is 72 hrs and which also requires intermittent work-up of volume reduction results in a substantial decrease in utilities, manpower and expenditure, thus making the process more convenient and economic.

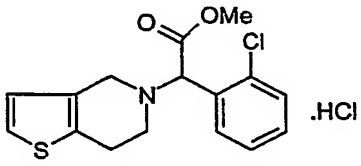
Accordingly in another embodiment the invention provides an improved process for the preparation of methyl (S)-(+)-alpha-(2-chlorophenyl)-6,7-dihydrothieno [3,2-c]pyridine-5(4H)-acetate (XIV), i.e., clopidogrel or its pharmaceutically acceptable salts,



(XIV)

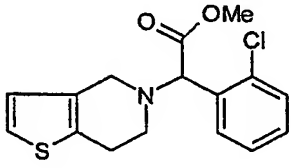
which comprises the steps of :

(a) condensing 4,5,6,7-tetrahydrothienopyridine hydrochloride (XV) with methyl α-bromo 2-chlorophenyl acetate (XVI) to give racemic methyl-alpha-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-acetate hydrochloride (XIII-A) by a method known per se;



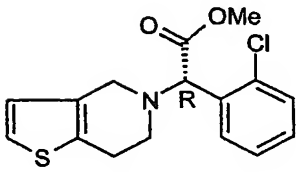
(XIII-A)

(b) treating the compound (XIII-A), thus obtained from step (a) with aqueous sodium bicarbonate in methylene chloride to obtain racemic methyl-alpha-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-acetate (II) by a method known per se;

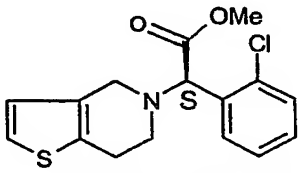


(II)

(c) resolving the racemic methyl-alpha-(2-chlorophenyl)-6,7-dihydrothieno [3,2-c]pyridine-5(4H)-acetate (II) by dissolving in a solvent, followed by addition of laevorotatory camphor-10-sulphonic acid to give the camphor sulphonate salt of methyl (R)-(-)-alpha-(2-chlorophenyl)-6,7-dihydrothieno [3,2-c]pyridine-5(4H)-acetate (III) and methyl (S)-(+)-alpha-(2-chlorophenyl)-6,7-dihydrothieno [3,2-c]pyridine-5(4H)-acetate (IV);



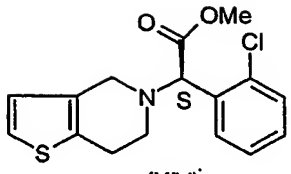
.camphor sulphonate
(III)



.camphor sulphonate
(IV)

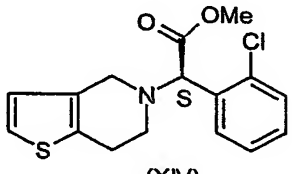
d) separating the two stereoisomers (III) and (IV);

(e) treating the camphor sulphonate salt of methyl (S)-(+)-alpha-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-acetate (IV) with aqueous sodium bicarbonate in methylene chloride to give methyl(S)-(+)-alpha-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-acetate (XIV) in a manner known per se;



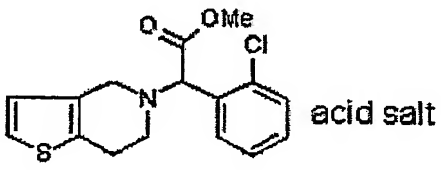
(XIV)

(f) treating the camphor sulphonate salt of methyl (R)-(-)-alpha-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-acetate (III) with liquor ammonia in methylene chloride to give methyl(R)-(-)-alpha-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-acetate (XII) in a manner known per se;



(XIV)

(g) racemization of methyl (R)-(-)-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate (XII) obtained from step (f) above by reacting with an acid in a solvent at the temperature range of 60-100° C to produce the racemic methyl-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate (XIII) acid salt.



(XIII)

(h) reacting methyl-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate (XIII) acid salt thus produced, with a base to produce the racemic methyl-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate (II) that is recycled for further resolution into (III) and (IV) according to step (c) above, for further production of (S)-(+)-clopidogrel;

(i) optionally converting methyl (S)-(+)-alpha-(2-chlorophenyl)-6,7-dihydrothieno [3,2-c]pyridine-5(4H)-acetate (XIV) to its pharmaceutically acceptable salts.

The invention further provides novel clopidogrel salts and pharmaceutical composition comprising them.

Thus, the present invention has the following advantages:

(1) Providing novel clopidogrel salts which are crystalline, non hygroscopic, easy to purify , isolate and store.

(2) Recycling the undesired R-isomer in the mother liquor by racemization increases the efficiency of the process by reducing wastage and renders the process more eco-friendly.

(3) Avoiding use of hazardous and expensive reagents like potassium tert-butoxide and sodium hydride.

(4) Minimizing the number of reaction steps.

(5) Reducing the time period of specific reaction steps and eliminating the associated work-up.

(6) The above factors result in a substantial decrease in utilities, manpower and expenditure, thus making the process more convenient and economic.

The novel pharmaceutically acceptable salts according to the present invention namely clopidogrel mesylate (clopidogrel methane sulfonic acid salt), clopidogrel hydroiodide, clopidogrel besylate, clopidogrel oxalate, clopidogrel trifluoroacetate, clopidogrel acetate, clopidogrel nitrate, clopidogrel perchlorate, clopidogrel phosphonate, clopidogrel benzoate, clopidogrel fumarate, clopidogrel maleate, clopidogrel citrate, clopidogrel tartrate, clopidogrel benzene sulfonate, clopidogrel gentisate, clopidogrel pamoate, clopidogrel palmitate, clopidogrel succinate, clopidogrel estolate, clopidogrel acistrate, clopidogrel stearate, clopidogrel propionate, clopidogrel hippurate, clopidogrel salicylate, clopidogrel methylsulfate, clopidogrel tannate, clopidogrel lauryl sulfonate, clopidogrel lactate, clopidogrel glutamate, clopidogrel trichloroacetate, clopidogrel maleate, clopidogrel glutarate, clopidogrel N-acetyl-L-glutamate, clopidogrel sulfate, clopidogrel gluconate and the like can be conveniently prepared by methods as described herein.

The clopidogrel salts can be prepared by using either of the strategies as mentioned below :

a) preparation of the desired salt by treatment with a base or

b) preparation of the desired salt by exchanging with another salt.

The solvent for the reaction to prepare pharmaceutically acceptable salt may be selected from the group comprising of alcohol, ester, ether, ketone and acetonitrile or a mixture thereof.

Alcohol as mentioned above, when used as reaction solvent may be selected from the group comprising of methanol, ethanol, n-propanol, isopropanol n-butanol and t-butanol.

Ketone when used as reaction solvent may be selected from the solvent such as acetone.

Ester when used as reaction solvent may be selected from the group comprising of ethyl acetate and butylacetate.

Ether when used as reaction solvent is tetrahydrofuran.

The solvent for the isolation is preferably ether. The ether may be selected from the group comprising of t-butyl methyl ether and di-isopropyl ether.

DETAILED DESCRIPTION OF THE INVENTION

In the following section preferred embodiments are described by way of examples to illustrate the process of this invention. However, this is not intended in any way to limit the scope of the present invention.

PREPARATORY EXAMPLES:

Example 1

Racemization of methyl (R)-(-)-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate (XII) :

Methyl (R)-(-)-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate (XII) (70 gm) added in to 280 ml of isopropyl alcohol and 25 ml of concentrated hydrochloric acid. The mixture was refluxed for 2 hours. Further, it was stirred for 3 hours at 0 to 5° C to form racemic methyl-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate hydrochloride salt. Solids filtered and washed with 25 ml of isopropyl alcohol to give 49 gm of racemic methyl-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate hydrochloride salt (XIII). (Yield: 62.9%)(Rotation: 0 ° to -1 °)

Example 2

Preparation of methyl-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate (II) :

49 gm of racemic methyl-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate hydrochloride salt (XIII) was suspended in 200 ml of water and adjusted pH 8 - 9 with liquor ammonia. Extracted with 175 ml of methylene chloride. Separated methylene chloride and evaporated to get 41 gm oil of racemic methyl-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate (II) (Yield: 89%)(Rotation: 0 ° to -1 °).

Methyl-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate (II) as received by above examples is further converted to clopidogrel bisulfate (I) by the manner known per se.

Example 3

Preparation of clopidogrel mesylate

In 2 lit 3-neck round-bottom flask 75 gm of clopidogrel (XIV) in 750 ml of methanol was dissolved at room temperature. To it, 20 gm of methane sulfonic acid was added. The reaction mixture was refluxed for 36 hours. Methanol was distilled under vacuum at 60 to 65°C. To the residue, tert-butyl methyl ether was added at room temperature and stirred to get the solid,

which was filtered under nitrogen and dried under vacuum to give 29 gm of clopidogrel mesylate.

IR (KBr, cm^{-1}):	1743, 1649, 1510, 1434, 1155 and 1042
^{1}H-NMR (DMSO d_6, 400 MHz):	7.60-7.64 (2H, m), 7.45-7.55 (2H, m), 7.38 (1H, d), 6.82 (1H, d), 5.51 (1H, s), 4.00-4.20 (2H, m), 3.72 (3H, s), 3.30-3.5 (2H, m), 3.0 (2H, s), 2.39 (3H, s)

Example 4

Preparation of clopidogrel hemisulfate (C_{16} H_{16} Cl NO_2 S. ½ H_2SO_4)

In 2 lit 3-neck round-bottom flask, 50 gm of clopidogrel bisulfate (I) and 38.3 gm of clopidogrel (XIV) in 500 ml of methanol was dissolved at room temperature. The reaction mixture was refluxed for 36 hours. Methanol was distilled out under vacuum at 60 to 65°C. To the residue, acetone was added at room temperature and stirred to get the solid, which was filtered under nitrogen and dried under vacuum to give 40 gm of clopidogrel hemisulfate.

Example 5

Preparation of clopidogrel acetate

In 2 lit 3-neck round-bottom flask, 50 gm of clopidogrel (XIV) in 500 ml of methanol was dissolved at room temperature. To it, 10 gm of acetic acid was

added. The reaction mixture was refluxed for 30 hours. Methanol was distilled under vacuum at 60 to 65°C. To the residue, n-hexane was added at room temperature, stirred and then decanted n-hexane. Distilled out n-hexane completely under vacuum at 60 to 65°C to get 40 gm of clopidogrel acetate.

Example 6

Preparation of racemic methyl-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate hydrochloride salt (XIII)

In a 10 lit 4-neck round-bottom flask, 500.0 gm of 4,5,6,7 tetrahydrothieno pyridine hydrochloride (XV), 681.5 gm of methyl-alpha-bromo 2-chlorophenyl acetate (XVI), 5.0 lit of dimethyl formamide and 850 gm of potassium carbonate were added and heated to a temperature of 80-85°C. Maintained at 80-85°C for 3 hrs and then cooled to 25-30°C. The reaction mixture was poured into 15.0 lit of water and 7.5 lit of methylene chloride was added with stirring. Methylene chloride layer was washed twice with 7.5 lit of water. The organic layer was dried over sodium sulphate. Distilled the organic layer under vacuum. Added 3.75 lit of acetone to the oily layer. Cooled to 5-10°C. 430.0 gm of concentrated hydrochloric acid was slowly added over a period of 30 minutes. Stirred at 25-30°C for 30 minutes. Cooled to a temperature of 5-10°C and further stirred for 2 hours at 10°C. Filtered the material under vacuum and washed with 750 ml of acetone and dried to obtain a crystalline solid (800.0 gm) of racemic methyl-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate hydrochloride (XIII).

Melting Point : 144°C

Example 7

Preparation of racemic methyl-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate (II)

In a 20-lit 4-neck round-bottom flask, 775.0 gm of racemic methyl-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate hydrochloride (XIII), 6.2 lit of methylene chloride and 3.1 lit of water were added followed by slow addition of 450.0 gm of sodium bicarbonate. Stirred for 1 hr. The methylene chloride layer was washed twice with 3.0 lit of water and dried over sodium sulphate under vacuum to get 675.0 gm of a thick viscous mass of racemic methyl-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate(II).

Example 8

Preparation of methyl-(S)-(+)-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate camphor sulphonate (IV), using isopropyl alcohol

In a 1 lit 4-neck round-bottom flask, 75.0 gm (0.233 moles) of racemic methyl-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate (II), 600.0 ml of isopropyl alcohol and 57.0 gm (0.2456 moles) of laevorotatory camphor-10-sulphonic acid were added under stirring. Stirred for 96 hrs at a temperature of 20-40° C. Filtered the product and washed with 100.0 ml isopropyl alcohol. Dried under vacuum for 1 hr. To it, 80.0 ml of isopropyl

alcohol was added, stirred at 50-55□C for 20 minutes, cooled to 25-30°C and maintained at 25-30°C for 6 hrs. Solid was filtered and washed with 25.0 ml of isopropyl alcohol. Subsequently dried at 20-40°C for 6 hr to give 21.0 gm of methyl-(S)-(+)-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate camphor sulphonate (IV).

Melting Point : 163°C

$[\alpha]_D^{20}$: +24.08° (c=1.68 g / 100 ml ; methanol)

Enantiomeric Purity by HPLC : 99.278%

Example 9

Preparation of methyl-(S)-(+)-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate camphor sulphonate (IV), using diglyme

In a 250 ml 4-neck round-bottom flask, 16.5 gm (0.0513 moles) of racemic methyl-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate (II) was dissolved in 82.5 ml of bis(2-methoxyethyl)ether (diglyme) and 5.96 gm (0.0256 moles) of laevorotatory camphor-10-sulfonic acid was added. Stirred for 49 hrs. The slurry was filtered and the cake was washed with 8 ml of bis(2-methoxyethyl)ether (diglyme) twice to get 7.7 gm of methyl-(S)-(+)-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate camphor sulphonate (IV).

Melting Point : 163.4°C

$[\alpha]_D^{20}$: +23.89°(c=1.68 g / 100 ml ; methanol)

Enantiomeric Purity by HPLC : 99.14%

Example 10

Preparation of methyl-(S)-(+)-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate (XIV)

7.7 gm of methyl-(S)-(+)-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate camphor sulphonate (IV) was suspended in 100 ml of water and saturated sodium bicarbonate solution was added till pH 8. The solution was then washed with 50 ml of methylene chloride. The methylene chloride layer was dried over sodium sulphate and concentrated to get 4.7 gm of methyl-(S)-(+)-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate (XIV).

Yield : 56 % (with respect to racemic base)

$[\alpha]_D^{20}$ = : +50.9°(c=1.61 g / 100 ml ; methanol)

Enantiomeric Purity by HPLC : 99.09%

Example 11

Preparation of methyl-(S)-(+)-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate (XIV)

In a 5 lit 4-neck round-bottom flask, 325 gm of methyl-(S)-(+)-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate camphor sulphonate (IV), 2.6 lit of methylene chloride and 1.3 lit of water were stirred for 5 minutes. 190 gm of sodium bicarbonate was slowly added and further stirred for 30 minutes. The methylene chloride layer was washed twice with

1.0 lit of water and dried over sodium sulphate. Distilled out methylene chloride completely under vacuum to obtain 185.0 gm of methyl-(S)-(+)-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate (XIV).

Yield : 54.81%(with respect to racemic base)

Example 11A

Preparation of methyl-(R)-(-)alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate(XII)

To 250 ml of mother liquor containing camphor sulphonate salt of methyl-(R)-(-)-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate (III) was added 500 ml of water and adjusted to pH 8 to 9 with liquor ammonia at 20 – 35°C. Added 350 ml of methylene chloride to the reaction mixture followed by extraction. Separated methylene chloride layer and washed with 2 x 200 ml water. Further, complete evaporation of methylene chloride gave 70 gm of methyl-(R)-(-)-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate (XII) as an oil.

Example 12

Preparation of clopidogrel hydroiodide

In a 50-litre 4-neck round-bottom flask, 20 lit of isopropyl alcohol was added to 1 kg of clopidogrel (XIV) followed by 0.724 kg of hydroiodic acid and kept at 20-25°C for 24 hrs. Filtered under vacuum, while washing with 6 lit of

isopropyl alcohol. The product was filtered under vacuum, while washing with 0.5 lit of ethanol. Finally dried under vacuum at 25-30°C for 12 hrs to obtain 0.9 kg of clopidogrel hydroiodide as a crystalline salt.

Clopidogrel hydroiodide thus produced is characterized by X-ray powder diffraction (XRPD) pattern with peaks at two-theta values (Values in parentheses indicate the lattice spacing in angstroms) at about : 3.7 ± 0.2 (23.592), 4.3 ± 0.2(20.441), 5.2 ± 0.2(16.895), 8.7 ± 0.2(10.072), 9.6 ± 0.2(9.179), 11.4 ± 0.2(7.693), 12.8 ± 0.2(6.862), 13.8 ± 0.2(6.396), 16.6 ± 0.2(5.334), 17.0 ± 0.2(5.191), 17.7 ± 0.2(4.983), 18.0 ± 0.2(4.899), 18.8 ± 0.2(4.715), 19.2 ± 0.2(4.596), 20.6 ± 0.2(4.292) at degrees 2θ.

Example 13

Preparation of clopidogrel mesylate

In a 10 litre 4-neck round-bottom flask, 6 lit of methanol was added to 1 kg of clopidogrel (XIV) under inert atmosphere (maintained throughout the procedure). Cooled to 5 -10°C. Slowly added 300.71 gm of methane sulphonic acid. The temperature was raised to 30-35°C and stirred for 12 hrs. Distilled out methanol completely under vacuum to obtain 1300.71 gm of solid clopidogrel mesylate.

Example 14

Preparation of clopidogrel perchlorate

In a 50 litre 4-neck round-bottom flask, 10 lit of methanol was added to 1 kg of clopidogrel (XIV) followed by slow addition of 0.447 kg of 70 % perchloric acid while maintaining the temperature at 10-15°C. Reaction mixture stirred for 12 hrs. Distilled out the methanol completely under vacuum. 15 lit of isopropyl alcohol and 500 ml of methanol was added and the reaction mixture was refluxed. Cooled to 25-30°C and filtered under vacuum, while washing the product with 2 lit of isopropyl alcohol. Finally, the product was dried under vacuum for 12 hrs to obtain 0.95 kg of clopidogrel perchlorate as a crystalline salt.

Clopidogrel perchlorate thus prepared is characterized by X-ray powder diffraction (XRPD) pattern with peaks at two-theta values (Values in parentheses indicate the lattice spacing in angstroms) at about: 7.9 ± 0.2 (11.059), 13.8 ± 0.2(6.413), 16.3 ± 0.2(5.414), 17.4 ± 0.2(5.084), 17.7 ± 0.2(5.006), 18.8 ± 0.2(4.718), 20.2 ± 0.2(4.385), 20.7 ± 0.2(4.287), 21.8 ± 0.2(4.059), 23.0 ± 0.2(3.853), 24.1 ± 0.2(3.678), 24.7 ± 0.2(3.606), 25.0 ± 0.2(3.550), 25.7 ± 0.2(3.462), 27.8 ± 0.2(3.205) degrees 2θ.

Example 15

Preparation of clopidogrel mesylate

In a 3 lit 3-neck round-bottom flask, 347.45 gm of clopidogrel (XIV) was reacted with 104.3183 gm of methane sulfonic acid in 1646.9 gm of methanol at 30-35°C followed by distillation of the methanol to prepare a solution of clopidogrel mesylate (645.553 gm). The sample of the solution was analyzed for the content of clopidogrel mesylate % w/w. The analysis indicated that clopidogrel mesylate was present in 69.68% w/w in methanol.

Further from the above solution, 100 gm of solution was removed and concentrated under reduced pressure at 30-35°C to give 69.68 gm of white to off-white crystalline powder (99.67%).

IR (KBr) cm^{-1} :	1748, 764, 710
^{1}H-NMR(400 MHz, DMSO d_6 + D_2O) :	6.83 – 7.66 (6H,m), 5.66 (1H, s), 4.15 – 4.31 (2H, m), 3.74 (3H, s) 3.45 – 3.60 (2H, m), 3.09 (2H, m), 2.39 (3H, s)
Mass peaks (m/z) :	322 (M+)

Example 16

Preparation of clopidogrel hydroiodide

In a 2 lit 3-neck round-bottom flask, 50 gm of clopidogrel (XIV) was reacted with 20.27 gm of 55% hydriodic acid in 300 ml of diethyl ether at 0-5°C to produce 35.0 gm of clopidogrel hydriodide (50.07%).

IR (KBr) cm^1 :	1744, 761, 725
^{1}H-NMR(400 MHz, DMSO d_6 + D_2O)□ :	6.85 – 7.66 (6H,m), 5.62 (1H, s), 4.13 – 4.28 (2H, m), 3.74 (3H, s) 3.42 – 3.55 (2H, m), 3.07 (2H, m)
Mass peaks (m/z) :	322 (M+)

Example 17

Preparation of clopidogrel perchlorate

In a 2 lit 3-neck round-bottom flask, 50 gm of clopidogrel (XIV) was dissolved in methanol at room temperature. To it, 23 gm of 70% perchloric acid was added. The reaction mixture was stirred at room temperature for 24 hrs and methanol was distilled under vacuum. Isopropyl alcohol was added at room temperature and the solid obtained was filtered and dried to give clopidogrel perchlorate, which melts at 168 – 170°C.

IR (KBr) cm^{-1} :	1752, 750, 703
^{1}H-NMR(400 MHz, DMSO d_6 + D_2O)□ :	6.83 – 7.65 (6H,m), 5.58 (1H, s), 4.09 – 4.24 (2H, m), 3.73 (3H, s) 3.37 – 3.54 (2H, m), 3.05(2H, m).
Mass peaks (m/z) :	322 (M+)

Example 18

Preparation of clopidogrel nitrate

In a 2 lit 3-neck round-bottom flask, 50 gm of clopidogrel (XIV) was reacted with 14.81 gm of concentrated nitric acid in 2.5 lit of diethyl ether at 0-5°C to produce 32.0 gm of clopidogrel nitrate (53.52%).

IR (KBr) cm^{-1} :	1749, 762, 719
^{1}H-NMR(400 MHz, DMSO d_6 + D_2O)□ :	6.85 – 7.66 (6H,m), 5.63 (1H, s), 4.14 – 4.29 (2H, m), 3.74 (3H, s) 3.43 – 3.55 (2H, m), 3.07(2H, m).
Mass peaks (m/z) :	322 (M+)

Though the new salts of instant invention can be prepared from any salt / form disclosed in the literature or by using the salts mentioned in the instant invention, preferably, the new salts can be prepared, using clopidogrel perchlorate obtained in the above example. This is especially to achieve the

higher purity / assay levels of the newly formed salt including the known salt such as bisulfate, hydrochloride, hydrobromide, taurocholate etc., which in turn are obtained from the higher purity / assay of clopidogrel perchlorate.

Pharmaceutical Compositions

The pharmaceutical compositions with novel salts of the invention as active ingredient may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels or aqueous or oily solutions or suspensions), for administration by inhalation (for example as finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, or intramuscular dosing or as a suppository (for rectal dosing).

The pharmaceutical compositions according to the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art.

Pharmaceutical compositions can be prepared from active ingredient, wherein the active ingredient is in a pure form or can also be in a solution form of desired concentration. The solution form can be in various organic solvents or mixtures thereof. Organic solvents can be selected from the group comprising of alcohols, halogenated solvents, ethers, amides, esters, ketones, hydrogenated solvents, acetonitrile, nitromethane and the like. The

examples of alcohols, halogenated solvents, ethers and amides that can be used are given below:

Alcohols	:	Methanol, Ethanol, n-Propanol, Isopropanol, n- Butanol, Tertiary-Butanol
Halogenated Solvents	:	Dichloromethane, Chloroform, Ethylenedichloride and the like
Ethers	:	Diethyl ether, Tertiary butyl dimethyl ether
Amides	:	N,N-dimethylformamide and the like

The active ingredients either in solid or solution form can be converted into pharmaceutical composition, wherein depending on the process of preparation of pharmaceutical composition, the solvent associated with Active Pharmaceutical Ingredient can be optionally removed before or during the process.

Suitable pharmaceutically acceptable excipients for a tablet formulation include for example, inert diluents such as lactose, spray dried anhydrous lactose, mannitol, spray dried mannitol, microcrystalline cellulose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch, hydroxy propyl cellulose (Klucel LF RTM), sodium starch glycolate, cross povidone, cross carmellose sodium or alginic acid; binding agents such as starch, povidone, hydroxypropylcellulose,

hydroxypropyl methylcellulose, gelatin, pregelatinised starch, lubricating agents such as magnesium stearate, stearic acid or talc, hydrogenated castor oil, colloidal silicon dioxide, preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid, citric acid and other organic acids, butylated hydroxyanisole, butylated hydroxytoluene, etc. The granules for the tablet can be prepared by using high or low shear granulator or fluid bed processor. The granules or pellets can also be prepared in extruders, merumeriser, rotor or wurster equipment. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal tract like enteric coating comprising polymers like cellulose acetate pthalate, hydroxypropyl methylcellulose pthalate, methacrylic acid copolymer type A, B or C (Eudragit L, Eudragit S or Eudragit L 30 D 55) , or to improve their stability and/or appearance, in either case, using conventional coating, agents and procedures well known in the art. The tablets may be coated with composition comprising polymers like ethylcellulose, hydroxypropyl methylcellulose, hydroxypropylcellulose, polyvinyl alcohol, Eudragit E 100 and combinations thereof in order to provide protection to the tablet core from the moisture. The tablets can be moisture protected by suitable excipients by making tablet in tablet where these excipients are present in outer coat.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, the capsule can filled with

granules or pellets. Compositions for oral use may be in the form of soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, or olive oil or can be filled as such.

Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxyethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with long chain alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl p-hydroxybenzoate, anti-oxidants (such as ascorbic acid) colouring agents, flavouring agents, and/or sweetening agents (such as sucrose, saccharin or aspartame).

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil (such as arachis oil, olive oil, sesame oil or coconut oil) or in a

mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those sets as above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally occurring gums such as gum acacia or gum tragacanth, naturally occurring phosphatides such as soya bean, lecithin, an esters, or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may be also contain sweetening, flavouring and preservative agents.

Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose and may also contain a demulcent, preservative, flavouring and/or coloring agent.

The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile or solvent, for example a solution in 1,2-butanediol.

Suppository formulations may be prepared by mixing the active ingredient with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Suitable excipients include, for example, cocoa butter and polyethylene glycols.

Topical formulations, such as creams, ointments, gels and aqueous or oily solutions or suspensions, may generally be obtained by formulating an active ingredient with a conventional, topically acceptable, vehicle or diluent using conventional procedure well known in the art.

Compositions for administration by inhalation may be in the form of a conventional pressurized aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or

hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

The amount of active ingredients that can be combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration.

In addition to the common dosage forms set out above, the compounds of the present invention may also be administered by controlled release means or delivery devices that are well known to those of ordinary skill in the art, such as those described in U.S. Patent Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123 4,008,719; 5, 674,533; 5,059,595; 5,591,767; 5,120,548; 5,073,543; 5,639,746; 5,354,556 and 5,733,566, the disclosures of which are each incorporated herein by express reference thereto. These pharmaceutical compositions can be used to provide slow or controlled release of one or more of the active ingredients therein using, for example, hydroxypropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems multiple layer coatings, microparticles, liposomes, microspheres, or like, or a combination thereof to provide the desired release profile in varying proportions.

Suitable controlled release formulations known to those of ordinary skill in the art, including those described herein may be readily selected for use with the pharmaceutical compositions of the invention. Thus, single unit dosage forms suitable for oral administration, such as tablets, capsules, gelcaps, caplets,

and the like, that are adapted for controlled-release are encompassed by the present invention.

The salts of the present invention, particularly clopidogrel hydroiodide and clopidogrel mesylate exhibit excellent flowability properties, as indicated by their low values of angle of repose and high values of tapped density. Tapped density is of great importance when one considers the high dose capsule product or the homogeneity of a low-dose formulation in which there are large differences in drug and excipient densities.

Tapped density is determined by the following procedure.

10 gm of the salt is weighed and transferred into a dry measuring cylinder. Stoppered the cylinder with rubber cork and kept it in the tapped density apparatus. Operated the apparatus for 50 taps. Measured the volume after tapping and calculated the tapped density.

Tapped density for clopidogrel hydroiodide is 0.991g/ml, which is higher than that of clopidogrel bisulphate *i.e.* 0.834 g/ml. Good flowability properties are essential for an efficient tabletting operation. A good flow of the powder or granulation to be compressed is necessary to assure efficient mixing and acceptable weight uniformity for the compressed tablets. Pharmaceutical powders have angle-of-repose values varying from 25 to 45°, with lower values indicating better flow characteristics. The angle of repose is determined by the following procedure.

A dry stainless steel funnel of length 14.0 cm, stem length of 8.0 cm, internal diameter 7.5 cm and an internal diameter of outflow opening of 0.8 cm. It is placed over a graph paper kept on a flat horizontal surface and fixed by a suitable device to maintain an upright position. Adjusted the distance between the lower end of the stem and the paper at 2.0 cm. The tip of the funnel was closed with the fore finger and the sample was poured along the side of the funnel upto the rim. The finger was removed to allow the sample to flow till the apex of the conical pile formed by the sample touches the lower end of the stem.

Marked the circle formed by the sample and calculated the radius from the observed diameter. Calculated the tan from the following equation.

$$\tan = \frac{\text{Distance between paper and lower end of funnel in cm}}{\text{Radius in cm}}$$

The angle of repose was calculated from the value of tan using the tangent table/scientific calculator.

The angle of repose for clopidogrel bisulphate is found to be 22.73°, which is less than 25°. On the other hand the angle of repose for clopidogrel hydroiodide is found to be 28.56°. These properties lead to better processabilty of these salts for preparing oral solid dosage formulations like tablets and hard gelatin capsules.

In the fasted state, pH of stomach is approximately 1.2 – 1.7. Past the pyloric sphincter between the stomach & duodenum the pH is about 4 - 5. Beyond

the proximal jejunum, pH is above 6. In fed conditions, the pH of the stomach may rise to 7. Dissolution in the pH of stomach will result in greater absorption from jejunum and ileum. The BCS allows estimation of likely contributions of three factors: dissolution, solubility and intestinal permeability, which affect oral drug absorption. The dissolution rate of drug can be controlled by changing the surface area and the solubility. One method of doing this is by changing the physical state as crystal form or salts *(Notari. R Absorption of Drugs from Gastrointestinal Tract in Biopharmaceutics and Clinical Pharmacokinetics and Introduction, 4th Edition, Marcel Decker, New York)*

The solubility data of the three salts of clopidogrel were generated in buffer of pH 1.2 and was found as given below in the Table.

Table

Medium	Clopidogrel bisulphate	Clopidogrel perchlorate	Clopidogrel hydroiodide	Clopidog-rel mesylate
Buffer pH = 1.2	30.68±2.0 mg/ml	5.95±0.5 mg/ml	62.77±5.0 mg/ml	204.17±10.0 mg/ml

At a pH of 1.2, the solubility of the mesylate and hydroiodide salt is significantly better than that of the bisulphate salt (the solubility for the mesylate, hydroiodide and bisulphate being 204.17 mg/dl, 62.77 mg/dl and 30.68 mg/dl respectively). From the data available it is expected that the

mesylate and hydroiodide salt will be more soluble than the bisulphate salt at the relevant human gastric pH (pH 1.2 – 1.8).

The dissolution and dissolution rate are related to the solubility. One can increase the absorption rate by increasing the dissolution rate *(Notari. R Absorption of Drugs from Gastrointestinal Tract in Biopharmaceutics and Clinical Pharmacokinetics and Introduction, 4th Edition, Marcel Decker, New York)*. Therefore, drug dissolution in aqueous media being a significant contributor in its oral absorption; drugs with greater solubility and dissolution have less chance of oral drug absorption problems.

The mesylate and the hydroiodide salts which are highly soluble at a pH of 1.2 will be more rapidly and completely absorbed in the stomach and the upper GI tract as compared to the bisulphate salt.

The above aspects of the invention are illustrated by way of examples.

Some pharmaceutical formulations of the medicine of the invention may be manufactured as per the following proposed non-restricting formulas:

(1) Tablets

Active ingredient equivalent to 75 mg base;

Excipients : lactose, microcrystalline cellulose, starch, povidone, magnesium stearate.

(2) Coated tablets

Active ingredient equivalent to 75 mg base;

Excipients : magnesium stearate, corn starch, gum Arabic, shellac, white sugar, glucose, white wax, carnauba wax, paraffin, new cochinealin

(3) Hard Gelatin Capsules

Active ingredient equivalent to 75 mg base;

Excipients: magnesium stearate, cornstarch, lactose, sodium starch glycolate

(4) Solution for injection

Active ingredient equivalent to 75 mg base;

isotonic solvent sufficient to make 3 ml

(5) Suppositories

Active ingredient equivalent to 75 mg base;

Semi-synthetic triglycerides sufficient to make 1 suppository.

(6) Soft Gelatin Capsules

Active ingredient equivalent to 75 mg base;

Excipients : polyethylene glycol, mentha oil, mono and di-glycerides, gelatin, sorbitol, glycerin, methyl paraben, propyl paraben, sodium lauryl sulphate.

Preparatory examples for pharmaceutical formulations of clopidogrel salts are given below.

Example 19

16.36 %w/w of microcrystalline cellulose (Avicel PH 112), 17.28%w/w mannitol (Pearlitol SD 200), 37.24 %w/w lactose anhydrous (Pharmatose DCL 21, RTM) and 2.39 %w/w cross povidone (Polyplasdone XL 10, RTM) were mixed and the mixture was granulated with 17.91 %w/w clopidogrel mesylate (dissolved in 1:1 v/v ratio of acetone and methylene chloride) and then dried. The granules were sized and mixed with 1.84 %w/w polyethylene glycol 6000, 0.92% w/w hydrogenated castor oil (Boricin Pharma, RTM), 0.92 %w/w colloidal silicon dioxide, 2.39 %w\w lactose anhydrous (Pharmatose DCL 21, RTM), 0.92 %w/w magnesium stearate, and 1.84 %w/w talc. This mixture was compressed to 544 mg weight tablets having a diameter of 11.11 mm. Results of various tests are given in Table 1.

Table 1

Tests	Result
Disintegration time	6-8 minutes
Organic volatile impurities	
Acetone	1064 ppm
Methylene chloride	317 ppm

Example 20

16.36 %w/w of microcrystalline cellulose (Avicel PH 112), 17.28%w/w mannitol (Pearlitol SD 200), 37.23 %w/w lactose anhydrous (Pharmatose DCL 21) and 2.39 %w/w cross povidone (Polyplasdone XL 10) were mixed and the mixture was granulated with 17.91 %w/w clopidogrel mesylate (65.29%w/w solution in acetone) and then dried. The granules were sized and mixed with 1.84 %w/w polyethylene glycol 6000, 0.92% w/w hydrogenated castor oil (Boricin Pharma), 0.92 %w/w colloidal silicon dioxide, 2.39 %w/w lactose anhydrous (Pharmatose DCL 21), 0.92 %w/w magnesium stearate, and 1.84 %w/w talc. This mixture was compressed to 544 mg weight tablets having a diameter of 11.11 mm.

Result of various tests are given in Table 2.

Table 2

Test	Result
Organic volatile impurities Acetone	2190 ppm

Example 21

16.36 %w/w of microcrystalline cellulose (Avicel PH 112), 17.28%w/w mannitol (Pearlitol SD 200), 37.23 %w/w lactose anhydrous (Pharmatose DCL 21) and 2.39 %w/w cross povidone (Polyplasdone XL 10) were mixed and the

mixture was granulated with 17.91 %w/w clopidogrel mesylate (69.68%w/w solution in methanol) and then dried. The granules are sized and mixed with 1.84 %w/w polyethylene glycol 6000, 0.92% w/w hydrogenated castor oil (Boricin Pharma), 0.92 %w/w colloidal silicon dioxide, 2.39 %w/w lactose anhydrous (Pharmatose DCL 21), 0.92 %w/w magnesium stearate, and 1.84 %w/w talc. This mixture was compressed to 544 mg weight tablets having a diameter of 11.11 mm.

Result of various tests are given in Table 3

Table 3

Test	Result
Organic volatile impurities Acetone	1400 ppm

Example 22

The tablets prepared in example 21 were film-coated with coating suspension prepared using composition given below. The film coating was performed using perforated coating pan apparatus. The approximate weight gain of the tablets was 5%w/w.

Ingredients	%w/w
HPMC E 15 LV	4,69
Ethylcellulose 10 cps	1,17
PEG 6000	0,47
Titanium Dioxide	0,81
Red Oxide of Iron	0,05
Methanol	34,74
Methylene Chloride	58,07

Result of various tests are given in Table 4.

Table 4

Test	Result
Disintegration time	14 minutes

Example 23

The tablets prepared in example 21 were film-coated with coating suspension prepared using composition given below. The film coating was performed using perforated coating pan apparatus. The approximate weight gain of the tablets was 3%w/w.

Ingredients	%w/w
HPMC E 15 LV	3,58
Magnesium stearate	0,89
PEG 6000	0,36
Titanium Dioxide	0,62
Red Oxide of Iron	0,04
Methanol	35,44
Methylene Chloride	59,07

Result of various tests are given in Table 5.

Table 5

Test	Result
Disintegration time	8-10 minutes

Example 24

The tablets prepared in example 21 were film-coated with coating suspension prepared using composition given below. The film coating using perforated coating pan apparatus. The approximate weight gain of the tablets was 3%w/w.

Ingredients	%w/w
HPMC E 15 LV	2,24
Ethylcellulose 10 cps	2,24
PEG 6000	0,36
Titanium Dioxide	0,62
Red Oxide of Iron	0,04
Methanol	35,44
Methylene Chloride	59,06

Result of various tests are given in Table 6.

Table 6

Test	Result
Disintegration time	18 minutes

Example 25

The granules prepared in example 21 were filled in hard gelatin capsules. The fill weight of the capsule was 544 mg.

Example 26

Part A- 26.81 %w/w of hydrated silica and 20.24%w/w lactose anhydrous (Pharmatose DCL 21) were mixed and the mixture was granulated with 44.69 %w/w clopidogrel mesylate (69.68%w/w solution in methanol) and then dried.

The granules are sized and mixed with 2.29 %w/w cross povidone (Polyplasdone XL 10), 4.59% w/w hydrogenated castor oil (Boricin Pharma), 0.46 %w/w lake of amaranth, and 0.92 %w/w talc. This mixture was compressed to 218 mg weight tablets having a diameter of 8.51 mm.

Part B- 48.75 %w/w of lactose anhydrous (Pharmatose DCL21), 48.7 %w/w of mannitol (Pearlitol SD 200), 1.14 %w/w of cross povidone (Polyplasdone XL 10), 1.14 %w/w of magnesium stearate and 0.23%w/w of colloidal silicon dioxide were mixed.

Tablet in tablet compression- The tablets compressed in part A and powder mixture prepared in part B were utilized to prepare tablet in tablet in which the powder mixture prepared in part B formed the outer portion or coating and the tablet prepared in part A formed the core. The total weight of the tablet was 800 mg and the tablet diameter was 12.7 mm.

Example 27

The tablets prepared in example 26 (part A) were film-coated with coating suspension prepared using composition given in example 23. The film coating

was performed using perforated coating pan apparatus. The approximate weight gain of the tablets was 3%w/w.

Example 28

26.81% w/w of hydrate of silica and 20.24% w/w of lactose anhydrous (Pharmatose DCL-21) were mixed and the mixture was granulated with 44.69% w/w clopidogrel mesylate (69.68% w/w solution in methanol) and then dried. The granules were sized through appropriate sieves and mixed with 4.58% w/w hydrogenated castor oil (Boricin Pharma), 2.29% w/w of cross povidone (polyplasdone XL10), 0.91% w/w of talc and 0.48% w/w of lake of carmosine. This mixture was compressed to 218 mg weight tablets.

Example: 29

The core tablets prepared in example 28 were compression coated with granules mixture (582 mg average wt)having following composition :

Ingredients	% w/w
Lactose anhydrous (Pharmatose DCL-21)	48,72
Mannitol (Pearlitol SD-200)	48,72
Cross povidone (Polyplasdone XL-10)	1,14
Magnesium stearate	1,14
Collodial silicon dioxide	0,28

Results of various tests are given in table 7.

Table 7

Tests	Results
Moisture content	6.0.% w/w
Disintegration time	8 – 9 minutes
Organic Volatile Impurities Methanol	321 ppm

Example 30

16.36% w/w of microcrystalline cellulose (Avicel PH-112), 17.27 % w/w mannitol (Pearlitol SD-200), 37.23% w/w lactose anhydrous (Pharmatose DCL-21) and 2.39% w/w cross povidone (Polyplasdone XL-10) were mixed and the mixture was granulated with 17.90% w/w clopidogrel mesylate (69.68% w/w solution in methanol) and then dried. The granules were sized through appropriate sieves and mixed with 1.84% w/w of hydrogenated castor oil (Boricin Pharma), 1.84% w/w of polyethylene glycol 6000, 0.92% w/w of colloidal silicon dioxide, 2.39% w/w of cross povidone (Polyplasdone XL-10) and 1.86 % w/w of talc. This mixture was compressed to 544 mg tablets having a diameter of 11.11 mm.

The compressed tablets were film coated with coating suspension prepared using composition given below. The film coating was performed by using perforated coating pan apparatus. The approximate weight gain of the tablets was 4 % w/w.

Ingredients	**% w/w**
HPMC E15 LV	2,98
Hydrogenated Castor Oil(Boricin Pharma)	0,72
DEP (Diethyl phthalate)	0,36
Titanium dioxide	0,50
Red Oxide of Iron	0,03
Methanol	35,82
Methylene chloride	59,68

Results of various tests are given in Table 8.

Table 8

Tests	Results
Assay %	101.73
RI (Related Impurities) %	
Single max.	2.07
Total impurities.	3.66
Organic Volatile Impurities	
Methanol	318 ppm
Methylene chloride	Nil.

Example 31

16.36% w/w of microcrystalline cellulose (Avicel PH-112), 17.27 % w/w mannitol (Pearlitol SD-200), 36.23% w/w lactose anhydrous (Pharmatose DCL-21) and 2.39% w/w cross povidone (Polyplasdone XL-10) were mixed and the mixture was granulated with a mixture of 1.01% w/w of citric acid anhydrous and 17.90% w/w clopidogrel mesylate (69.68% w/w solution in methanol) and then dried. The granules were sized through appropriate sieves and mixed with 1.84% w/w of hydrogenated castor oil (Boricin Pharma), 1.84% w/w of polyethylene glycol 6000, 0.92% w/w of colloidal silicon dioxide, 2.39% w/w of cross povidone (Polyplasdone XL-10) and 1.85 % w/w of talc. This mixture was compressed to 544 mg tablets having a diameter of 11.11 mm.

The compressed tablets were film coated with coating suspension prepared using composition given below. The film coating was performed by using perforated coating pan apparatus. The approximate weight gain of the tablets was 3.67%.

Ingredients	**% w/w**
HPMC E15 LV	2,98
Hydrogenated castor oil(Boricin Pharma)	0,72
PEG 6000	0,36
Titanium dioxide	0,50
Red Oxide of Iron	0,03
Methanol	35,82
Methylene chloride	59,68

Results of various tests are given in Table 9.

Table 9

Tests	Results
Disintegration time	9 – 10 min
Assay %	100.17
RI (Related Impurities) %	
Single max.	0.26
Total impurities	0.85
Organic Volatile Impurities	
Methanol	Nil
Acetone	129 ppm
Methylene chloride	Nil

Example 32

36.08% w/w of clopidogrel mesylate, 17.41 % w/w mannitol (Pearlitol SD200), 21.23% w/w lactose anhydrous (Pharmatose DCL-21), 16.48% w/w microcrystalline cellulose (Avicel PH 112), 2.40% w/w of cross povidone (Polyplasdone XL-10), 1.85% w/w of polyethylene glycol (PEG-6000), 1.85% w/w of hydrogenated castor oil (Boricin Pharma) and 0.74 w/w of colloidal silicon dioxide and 1.85% w/w of talc were sifted through appropriate sieve and then mixed. The mixed blend was compressed into tablets of 270 mg weight on Rotary tablet KORSCH machine using 12/32" Standard Concave punches.

Coating : The compressed tablets were film coated with coating suspension prepared using composition given in example 31. The film coating was performed using perforated coating pan apparatus. The approximate weight gain of the tablets was 3.70 % w/w.

Results of various tests are given in Table 10.

Table 10

Tests	Results
Assay %	106.19%
Related Impurities %	
Single Max	0.17%
Total Impurities	1.50%
Dissolution in 45 minutes (USP-II:900 ml: 50rpm :0.1M HCl)	100.59 %
Water by KF %	3.52%
Disintegration Time	5 min 19 sec
Organic Volatile Impurities	
Methanol	Nil
Methylene Chloride	66 ppm

Example 33

36.08% w/w of clopidogrel mesylate , 17.41 % w/w mannitol (Pearlitol SD 200), 20.40% w/w lactose anhydrous (Pharmatose DCL-21), 16.48% w/w microcrystalline cellulose (Avicel-112), 2.40% w/w of cross povidone (Polyplasdone XL-10), 1.85% w/w of polyethylene glycol (PEG-6000), 1.85%

w/w of hydrogenated castor oil (Boricin Pharma), 0.74 w/w of colloidal silicon dioxide and 1.85% w/w of talc & 0.93% w/w of magnesium stearate were sifted through appropriate sieve and then mixed. The mixed blend was compressed into tablets of 270 mg weight on Rotary tablet KORSCH machine using 12/32" Standard Concave punches.

The compressed tablets were film coated with coating suspension prepared using composition given in example 31. The approximate weight gain of the tablets was 4.44 % w/w.

Results of various tests are given in Table 11.

Table 11

Tests	Results
Assay %	99.45
Related Impurities %	
Single Max	0.37
Total Impurities	2.38
Dissolution in 45 minutes (USP-II:900 ml: 50rpm :0.1M HCl)	103.44 %
Water by KF %	4.90 %
Disintegration Time	5 min 40 Sec
Organic Volatile Impurities	
Methanol	Nil
Methylene chloride	184 ppm

Example 34

36.08% w/w of clopidogrel mesylate, 30.06% w/w lactose anhydrous (Pharmatose DCL-2),25.18% w/w microcrystalline cellulose (Avicel PH 112), 2.40% w/w of cross povidone (Polyplasdone XL-10), 1.85% w/w of polyethylene glycol (PEG-6000), 0.92% w/w of hydrogenated castor oil (Boricin Pharma), 0.74 w/w of colloidal silicon dioxide and 1.85% w/w of talc & 0.92% w/w of magnesium stearate were sifted through appropriate sieve and then mixed. The mixed blend was compressed into tablets of 270 mg weight on Rotary tablet KORSCH machine using 12/32" Standard Concave punches.

The compressed tablets were film coated with coating suspension prepared using composition given in example 31. The approximate weight gain of the tablets was 3.2 % w/w.

Results of various tests for uncoated tablets are given in table 12.

Table 12

Tests	Results
Assay %	97.36
RI (Related Impurities) %	
Single max.	0.28
Total impurities.	0.88
Disintegration time	3-4 min

Example 35

36.08% w/w of clopidogrel mesylate, 28.74% w/w mannitol (Pearlitol SD200),26.50% w/w microcrystalline cellulose (Avicel PH 112), 2.40% w/w of cross povidone (Polyplasdone XL-10), 1.85% w/w of polyethylene glycol (PEG-6000), 0.92% w/w of hydrogenated castor oil (Boricin Pharma), 0.74 w/w of colloidal silicon dioxide and 1.85% w/w of talc & 0.92% w/w of magnesium stearate were sifted through appropriate sieve and then mixed. The mixed blend was compressed into tablets of 270 mg weight on Rotary tablet KORSCH machine using 12/32" Standard Concave punches.

Results of various tests for uncoated tablets are given in table 13.

Table 13

Tests	Results
Assay %	99.43
RI (Related Impurities) %	
Single max.	0.29
Total impurities	0.86
Disintegration time	5-6 min

Example 36

36.08% w/w of clopidogrel mesylate, 25.64% w/w of mannitol (Pearlitol SD 200), 29.57% w/w lactose anhydrous (Pharmatose DCL-21), 2.40% w/w of cross povidone (Polyplasdone XL-10), 1.85% w/w of polyethylene glycol

(PEG-6000), 0.92% w/w of hydrogenated castor oil (Boricin Pharma), 0.74 w/w of colloidal silicon dioxide and 1.85% w/w of talc & 0.92% w/w of magnesium stearate were sifted through appropriate sieve and then mixed. The mixed blend was compressed into tablets of 270 mg weight on Rotary tablet KORSCH machine using 12/32" Standard Concave punches.

Results of various tests for uncoated tablets are given in Table 14.

Table 14

Tests	Results
Assay %	102.19
RI (Related Impurities) %	
Single max.	0.19
Total impurities.	0.60
Disintegration time	5-6 min

Example 37

19.47 % w/w of lactose anhydrous (Pharmatose DCL-21), 17.40% w/w of mannitol (Pearlitol SD 200), 16.48% w/w of microcrystalline cellulose (Avicel PH 112) was mixed and the mixture was granulated using 1.85% w/w of citric acid anhydrous (dissolved in methanol 10 %w/v) and then dried. The granules were dried and mixed with 36.08% w/w of clopidogrel mesylate, 2.40% w/w of cross povidone (Polyplasdone XL-10), 1.85% w/w of polyethylene glycol (PEG-6000), 0.92% w/w of hydrogenated castor oil (Boricin Pharma), 0.74 w/w of colloidal silicon dioxide and 1.85% w/w of talc & 0.92% w/w of

magnesium stearate were sifted through appropriate sieve and then mixed. The mixed blend was compressed into tablets of 270 mg weight on Rotary tablet KORSCH machine using 12/32" Standard Concave punches.

Results of various tests for uncoated tablets are given in Table 15.

Table 15

Tests	Results
Assay %	101.99
RI (Related Impurities) %	
Single max.	0.12
Total impurities.	0.45
Disintegration time	5-6 min

The compressed tablets were film coated with coating suspension prepared using composition given in example 31. The approximate weight gain of the tablets was 3.33 % w/w. The results of various tests are given in Table 16.

Table 16

Tests	Results
Assay %	101.74
Related Impurities	
Single Max.	0.50
Total Impurities	1.27
Dissolution in 45 minutes (USP-II:900 ml: 50rpm :0.1M HCl)	109.93
Water by KF %	3.68
Disintegration Time	8 min 32 sec
Organic Volatile Impurities	
Methanol	143
Methylene chloride	Nil

Example 38

17.64 % w/w of lactose anhydrous (Pharmatose DCL-21), 15.77% w/w of Mannitol (Pearlitol SD 200), 14.93% w/w of microcrystalline cellulose (Avicel PH 112) was mixed and the mixture was granulated using 1.67% w/w of citric acid anhydrous and 0.03% w/w of butylated hydroxy toluene (BHT) then dried. The granules were dried and mixed with 32.69% w/w of clopidogrel mesylate, 2.52% w/w of cross povidone (Polyplasdone XL-10), 3.35% w/w of polyethylene glycol (PEG-6000), 10.06% w/w of hydrogenated castor oil (Boricin Pharma), 1.34 w/w of colloidal silicon dioxide and 1.85% w/w of talc &

0.92% w/w of magnesium stearate, sifted through standard sieve and then mixed. The mixed blend was compressed into tablets of 270 mg weight on Rotary tablet KORSCH machine using 12/32" Standard Concave punches.

Results of various tests for uncoated tablets are given in Table 17.

Table 17

Tests	Results
Assay %	98.63
Related Impurities	
Single Max.	0.33
Total Impurities	0.86
Dissolution in 45 minutes (USP-II:900 ml: 50rpm :0.1M HCl)	107.02
Water by KF %	3.41
Disintegration Time	16 min 25 sec
Organic Volatile Impurities	
Methanol	136
Methylene chloride	Nil

CAPSULE FORMULATIONS:

Example 39

39.23% of lactose anhydrous (Pharmatose DCL 21), 17.72 of microcrystalline cellulose (Avicel PH 112) and 8.73% w/w of mannitol (Pearlitol SD 200) were mixed and granulated with 1.09 % w/w of citric acid anhydrous (dissolved in methanol 10 %w/v solution). The dried and sized granules were mixed with

23.2 % w/w of clopidogrel mesylate. The mixed blend was filled in hard gelatin capsule of size "00". The fill weight of capsule was 420 mg. The results of various test are given in Table 18.

Table 18

Tests	Results
Related Impurities Single Max. Total Impurities	 0.16 0.58
KF %	2.51
Dissolution in 45 minutes (USP-II : 900 ml : 50rpm : 0.1M HCl)	103.45%
Disintegration Time	2 min 4 sec

Example 40

23.36% of lactose anhydrous (Pharmatose DCL 21), 18.05% w/w of microcrystalline cellulose (Avicel – 112), 19.06% w/w of mannitol (Pearlitol SD 200) and 39.52 % w/w of clopidogrel mesylate were mixed. The mixed blend was filled in hard gelatin capsule of size "1". The fill weight of capsule was 246.5mg. The results of various tests are given in Table 19

Table 19

Tests	Results
Assay %	107.33%
Related Impurities Single Max. Total Impurities	 0.13 0.55
KF %	3.14
Dissolution (USP-II : 900 ml : 50rpm : 0.1M HCl)	88.64%
Disintegration Time	2 min 4 sec

Example 41

38.83 % w/w of clopidogrel hydroiodide, 18.58 % w/w of lactose anhydrous (Pharmatose DCL-21), 17.41% w/w of mannitol (Pearlitol SD 200), 16.48% w/w of microcrystalline cellulose (Avicel-112), 2.40 % w/w of cross povidone (Polyplasdone XL 10), 1.85% w/w of polyethylene glycol (PEG-6000), 0.93% w/w of hydrogenated castor oil (Boricin Pharma), 0.74 w/w of colloidal silicon dioxide, 1.85% w/w of talc and 0.93% w/w of magnesium stearate were mixed after sifting through appropiate sieves. The mixed blend was compressed into tablets of 270 mg weight on Rotary tablet KORSCH machine using 12/32" Standard Concave punches. Disintegration time of the tablet is 1 – 2 minutes.

The compressed tablets were film coated with coating suspension prepared using composition given in example 31.The approximate weight gain of the tablets was 3.2 % w/w. The results of various tests are given in Table 20.

Table 20

Tests	Results
Assay %	98.96
Related Impurities	
Single Max.	0.10
Total Impurities	0.64
Dissolution in 45 minutes (USP-II:900 ml: 50rpm :0.1M HCl)	98.67
Water by KF %	3.19
Disintegration Time	1-2 Min
Organic Volatile Impurities	
Methanol	Nil
Methylene chloride	71

Example 42

48.54 % w/w of clopidogrel hydroiodide, 45.21% w/w of microcrystalline cellulose (Avicel PH-112), 1.16% w/w pregelatinized starch (Lycatab C), 4.63% w/w of hydrogenated castor oil (CUTINA HR) and 0.46 w/w of colloidal silicon dioxide, were sifted through appropiate sieve and mixed. The mixed blend was compressed into tablets of 215 mg weight on Rotary tablet

KORSCH machine using 11/32" Standard Concave punches. Disintegration time of the tablet is 1 minute.

Table 21

Tests	Results
Assay %	102.78
Related Impurities	
Single Max.	0.06
Total Impurities	0.17
Dissolution in 45 minutes (USP-II:900 ml: 50rpm :0.1M HCl)	2.91%
Disintegration Time	1 min

Example 43

51.14 % w/w of clopidogrel hydroiodide, 38.61% w/w of microcrystalline cellulose (Avicel PH – 112), 4.88 % w/w of hydrogenated castor oil (Boricin Pharma), 4.88 % w/w of hydroxypropylcellulose (HPC-L11) and 0.48 w/w of colloidal silicon dioxide, were sifted through appropiate sieve and mixed. The mixed blend was compressed into tablets of 205 mg weight on Rotary tablet KORSCH machine using 11/32" Standard Concave punches. Disintegration time of the tablet is 1 minute.

The results of various tests are given in table 22.

Table 22

Tests	Results
Assay %	100.88
Related Impurities (%) Single Max. Total Impurities	 0.06 0.18
Dissolution in 45 minutes (USP-II : 900 ml :50 rpm :0.1 M HCl)	2.85%
Disintegration Time	1 min

Example 44

The tablets prepared in example 42 & example 43 were film coated with coating suspension prepared using composition given below. The film coating was performed using perforated coating pan apparatus. The approximate weight gain of the tablet was 3 % w/w.

Ingredients	% w/w
Hydroxy propyl cellulose (Kulcel LF)	3,23
Polyethylene glycol – 6000	0,32
Titanium Dioxide	0,49
Red Oxide of Iron	0,03
Methanol	95,98

Results of various tests for tablets are given in Table 23.

Table 23

Tests/ example	Example 42	Example 43
Assay %	102.4	102.76
Related Impurities		
Single Maximum	0.06	0.06
Total Impurities	0.11	0.17
KF %	2.86	2.83
Dissolution in 45 minutes (USP-II : 900 ml : 50 rpm : 0.1 M HCl)	100.68	102.58
Disintegration Time	50 sec	50 sec
Other voluble impurities		
Methanol	268	238
Methylene chloride	Nil	Nil

Example 45

58.24 % w/w of clopidogrel hydroiodide and 41.76% w/w of microcrystalline cellulose (Avicel-112) was sifted and mixed. The mixed blend was filled in hard gelatin capsules of size "2". The fill weight of the capsule was 180 mg. Results of various tests are given in Table 24

Table 24

Tests	Results
Assay %	103.32
Related Impurities Single Maximum Total Impurities	 0.20 0.71
KF %	2.53
Dissolution in 45 minutes (USP-II : 900 ml : 50 rpm : 0.1 M HCl)	97.47
Disintegration Time	1 min 28 sec

Example 46

52.42 % w/w of clopidogrel hydroiodide and 41.58% w/w of mannitol (Pearlitol SD 200) was sifted through appropiate sieves and mixed. The mixed blend was filled in hard gelatin capsules of size "2". The fill weight of the capsule was 200 mg. Result of various tests are given in Table 25.

Table 25

Tests	Results
Assay %	121.86
Related Impurities	
Single Maximum	0.06
Total Impurities	0.17
KF %	0.34
Dissolution in 45 minutes (USP-II : 900 ml : 50 rpm : 0.1 M HCl)	98.59
Disintegration Time	2 min 4 sec

Example 47

Comparative dissolution profile of clopidogrel bisulphate, clopidogrel hydroiodide and clopidogrel mesylate at various pH. Dissolution profile at pH 2.1 is given in Table 26 and dissolution profile at pH 4.5 is given in Table 27.

Table 26

pH 2.1 simulated gatric fluid fasted

Apparatus : USP apparatus (IL) (paddles)

RPM : 50

Volume : 900 ml

		% Drug Release at Different Time Intervals					
Salt		5 min	10 min	15 min	20 min	30 min	45 min
1	Clopidogrel bisulphate	12.14	80.88	81.85	82.52	82.46	83.22
2	Clopidogrel hydroiodide	94.36	102.30	103.69	104.32	102.75	105.06

Table 27

pH 4.5 acetate buffer

Apparatus : USP apparatus (IL) (paddles)

RPM : 50

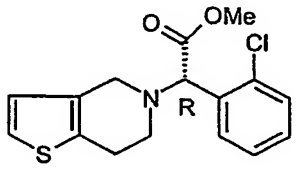
Volume : 900 ml

		% Drug Release at Different Time Intervals					
Salt		5 min	10 min	15 min	20 min	30 min	45 min
1	Clopidogrel bisulphate	1.22	1.55	8.99	12.92	15.15	18.17
02	Clopidogrel hydroiodide	10.06	12.29	15.10	18.46	22.59	27.93

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

Claims

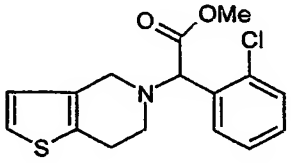
1. A process for racemization of methyl (R)-(-)-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate (XII)



(XII)

which comprises the steps of :

(a) reacting methyl (R)-(-)-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate (XII) with acid in a solvent at a temperature range of 60-100° C to produce the racemic methyl -alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine - 5(4H)-acetate acid salt (XIII)

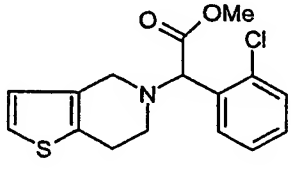


acid salt

(XIII)

and

(b)reacting methyl-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2- c] pyridine-5(4H)-acetate acid salt (XIII) thus produced with a base to produce the racemic methyl-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate (II).



(II)

2. The process as claimed in claim 1, where the acid used in the step (a) is selected from the group consisting of HCl, H_2SO_4, CH_3COOH and H_3PO_4.

3. The process as claimed in claim 2, wherein said acid is selected from HCl or H_2SO_4.

4. The process as claimed in claim 3, wherein said acid is HCl

5. The process as claimed in claim 1, wherein said solvent used in the step (a) is selected form the group consisting of methanol, ethanol, isopropyl alcohol, n-butanol and tert-butanol.

6. The process as claimed in claim 5, wherein said solvent is isopropyl alcohol.

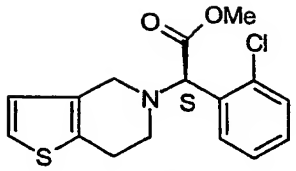
7. The process as claimed in claim 1 , wherein the base used in the step (b) is selected from the group consisting of sodium hydroxide, potassium hydroxide, sodium ethoxide, liquor ammonia, triethyl amine, diethyl amine and monomethyl amine.

8. The process as claimed in claim 7, wherein said base is liquor ammonia.

9. The process as claimed in claim 1, wherein the reaction step (a) is carried out for 30 minutes to 4 hrs.

10. The process as claimed in claim 9, wherein the reaction step (b) is carried out for 15 minutes to 45 minutes.

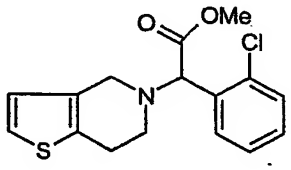
11. An improved process for the preparation of methyl (S)-(+)-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate (XIV) i.e. clopidfogrel or its pharmaceutically acceptable salt,



(XIV)

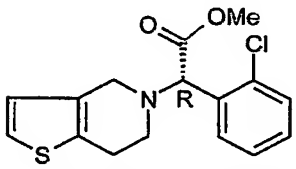
which comprises the steps of:

(a) resolving methyl-alpha-(2-chlorophenyl)-6,7-dihydro- thieno [3,2- c]pyridine-5(4H)-acetate (II)

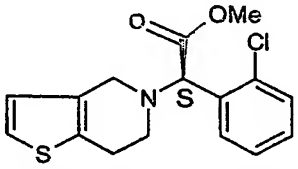


(II)

with laevorotatory camphor-10-sulfonic acid to give methyl (R)-(-) alpha- (2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-4(4H)-acetate camphor sulfonic acid salt (III) and methyl (S)-(+)alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-4(4H)-acetate camphor sulfonic acid salt (IV)



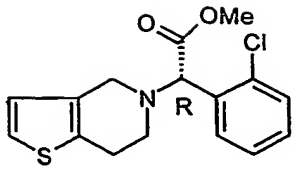
.camphor sulphonate
(III)



.camphor sulphonate
(IV)

(b) separating the two stereoisomers (III) and (IV)

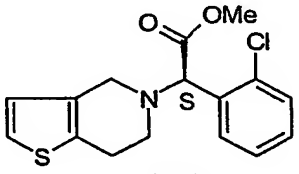
(c) converting the (-) stereoisomer (III) into methyl (R)-(-)alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-4(4H)-acetate (XII)



(XII)

by using liquor ammonia in methylene chloride ;

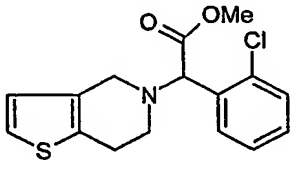
(d) converting (+) stereoisomer (IV) above to methyl (S)-(+)alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-4(4H)-acetate (XIV)



(XIV)

by using aqueous sodium bicarbonate in dichloromethane ;

(e) racemization of methyl (R)-(-)-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate (XII) by reacting methyl (R)-(-)-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate (XII) with an acid in a solvent at a temperature range of 60-100° C to produce the racemic methyl -alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate acid salt (XIII);



acid salt

(XIII)

(f) reacting methyl-alpha-(2-chlorophenyl)-6,7-dihydro-thieno [3,2-c] pyridine-5(4H)-acetate acid salt (XIII) thus produced with a

base to produce the racemic methyl-alpha-(2chlorophenyl) -6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate (II) that is recycled for further resolution into its its (+) and (-) stereo isomer according to step(a) above for further production of target compound (XIV) i.e. clopidogrel and

(g) optionally converting methyl-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c] pyridine-5(4H)-acetate(XIV) to its pharmaceutically acceptable in a manner known per se.

12. The process as claimed in claim 11, wherein the acid used in the step (e) is selected from the group consisting of HCl, H_2SO_4, CH_3COOH and H_3PO_4.

13. The process as claimed in claim 12, wherein said acid is selected from HCl or H_2SO_4.

14. The process as claimed in claim 13, wherein said acid is HCl.

15. The process as claimed in claim 11 ,wherein said solvent used in the step (e) is selected form the group consisting of methanol, ethanol, isopropyl alcohol, n-butanol and tert-butanol.

16. The process as claimed in claim 15, wherein said solvent is isopropyl alcohol.

17. The process as claimed in claim 11 , wherein the base used in the step (f) is selected from the group consisting of sodium hydroxide, potassium hydroxide, sodium ethoxide, liquor ammonia, triethyl amine, diethyl amine and monomethyl amine.

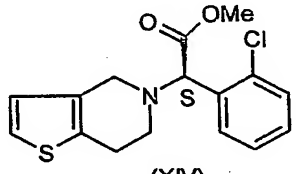
18. The process as claimed in claim 17, wherein said base is liquor ammonia

19. The process as claimed in claim 11 , wherein the reaction step (e) is carried out for 30 minutes to 4 hrs.

20. The process as claimed in claim 11, wherein the reaction step (f) is carried out for 15 minutes to 45 minutes.

21. The process as claimed in claim 11, wherein said pharmaceutically acceptable sallts of clopidogrel is selected from the group consisting of bisulphate,mesylate, besylate, hemisulfate, tosylate, oxalate, trifluoroacetate, acetate, nitrate, perchlorate and phosphonate .

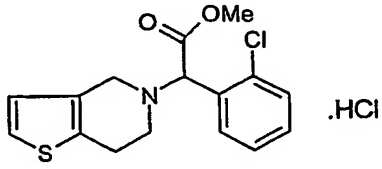
22. An improved process for the preparation of methyl (S)-(+)-alpha-(2-chlorophenyl)-6,7-dihydrothieno [3,2-c]pyridine-5(4H)-acetate (XIV), i.e., clopidogrel or its pharmaceutically acceptable salts,



(XIV)

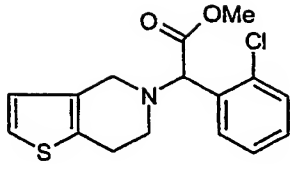
which comprises the steps of :

(a) condensing 4,5,6,7-tetrahydrothienopyridine hydrochloride (XV) with methyl α-bromo 2-chlorophenyl acetate (XVI) to give racemic methyl-alpha-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-acetate hydrochloride (XIII-A) by a method known per se;



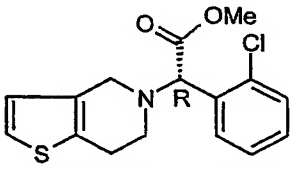
(XIII-A)

(b) treating the compound (XIII-A), thus obtained from step (a) with aqueous sodium bicarbonate in methylene chloride to obtain racemic methyl-alpha-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-acetate (II) by a method known per se;

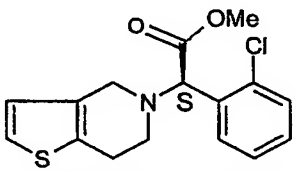


(II)

(c) resolving the racemic methyl-alpha-(2-chlorophenyl)-6,7-dihydrothieno [3,2-c]pyridine-5(4H)-acetate (II) by dissolving in a solvent, followed by addition of laevorotatory camphor-10-sulphonic acid to give the camphor sulphonate salt of methyl (R)-(-)-alpha-(2-chlorophenyl)-6,7-dihydrothieno [3,2-c]pyridine-5(4H)-acetate (III) and methyl (S)-(+)-alpha-(2-chlorophenyl)-6,7-dihydrothieno [3,2-c]pyridine-5(4H)-acetate (IV);



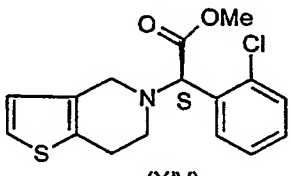
.camphor sulphonate
(III)



.camphor sulphonate
(IV)

(d) separating the two stereoisomers (III) and (IV);

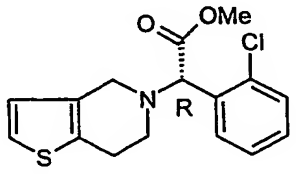
(e) treating the camphor sulphonate salt of methyl (S)-(+)-alpha-(2-chlorophenyl)-6,7-dihydrothieno [3,2-c]pyridine-5(4H)-acetate (IV) with aqueous sodium bicarbonate in methylene chloride to give methyl (S)-(+)-alpha-(2-chlorophenyl)-6,7-dihydrothieno [3,2-c]pyridine-5(4H)-acetate (XIV) in a manner known per se;



(XIV)

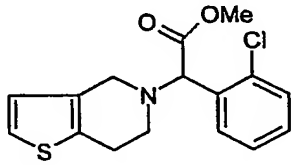
(f) treating the camphor sulphonate salt of methyl (R)-(-)-alpha-(2-chlorophenyl)-6,7-dihydrothieno [3,2-c]pyridine-5(4H)-acetate (III) with liquor ammonia in methylene chloride to give methyl

(R)-(-)-alpha-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-acetate (XII) in a manner known per se;



(XII)

(g) racemization of methyl (R)-(-)-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate (XII) obtained from step (f) above by reacting with an acid in a solvent at the temperature range of 60-100° C to produce the racemic methyl-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate (XIII) acid salt;



acid salt

(XIII)

(h) reacting methyl-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate (XIII) acid salt thus produced, with a base to produce the racemic methyl-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate (II) that is recycled for further resolution into (III) and (IV) according to step (c) above, for further production of (S)-(+)-clopidogrel and

(i) optionally converting methyl (S)-(+)-alpha-(2-chlorophenyl)-6,7-dihydrothieno [3,2-c]pyridine-5(4H)-acetate (XIV) to its pharmaceutically acceptable salts.

23. The process as claimed in claim 22, wherein said solvent used for the resolution in step (c) is an alkoxy substituted acyclic ether.

24. The process as claimed in claim 23, wherein alkoxy substituted acyclic ether is R-O-R'-O-R'-O-R, wherein R' = - CH_2 - CH_2 -, R is C_1 - C_3 alkyl.

25. The process as claimed in claim 24, wherein R is methyl.

26. The process as claimed in claim 23,wherein the alkoxy substituted acyclic ether used as solvent is CH_3-O-CH_2-CH_2-O-CH_2-CH_2-O-CH_3 *i.e.*, bis(2-methoxyethyl)ether.

27. The process as claimed in claim 22, wherein the reaction in step(b) is carried out for is 48 hrs.

28. The process as claimed in claim 22, where the acid used in the step (g) is selected from the group consisting of HCl, H_2SO_4, CH_3COOH and H_3PO_4.

29. The process as claimed in claim 28, wherein said acid is selected from HCl or H_2SO_4.

30. The process as claimed in claim 29, wherein said acid is HCl

31. The process as claimed in claim 22, wherein said solvent used in the step (g) is selected from the group consisting of methanol, ethanol, isopropyl alcohol, n-butanol and tert-butanol.

32. The process as claimed in claim 31, wherein said solvent is isopropyl alcohol.

33. The process as claimed in claim 22, wherein the base used in the step (h) is selected from the group consisting of sodium hydroxide, potassium hydroxide, sodium ethoxide, liquor ammonia, triethyl amine, diethyl amine and monomethyl amine.

34. The process as claimed in claim 33, wherein said base is liquor ammonia.

35. The process as claimed in claim 22 , wherein the reaction step (g) is carried out for 30 minutes to 4 hrs.

36. The process as claimed in claim 35, wherein the reaction step (h) is carried out for 15 minutes to 45 minutes.

37. The process as claimed in claim 22 , wherein said pharmaceutically acceptable salt is selected from the group consisting of mesylate (clopidogrel methane sulfonic acid salt), hydroiodide, besylate, oxalate, trifluoroacetate, acetate, nitrate, perchlorate, phosphonate, benzoate, fumarate, maleate, citrate, tartrate, benzene sulfonate, gentisate, pamoate, palmitate, succinate, estolate, acistrate, stearate, propionate, hippurate, salicylate, methylsulfate, tannate, lauryl sulfonate, lactate, glutamate, trichloroacetate, maleate, glutarate, N-acetyl-L-glutamate, sulfate and gluconate.

38. The process as claimed in claim 37, wherein the salt thus obtained in non-hygroscopic and crystalline in nature.

39. The process as claimed in claim 37, wherein said pharmaceutically acceptable salt of clopidogrel is prepared by treatment with a corresponding base.

40. The process as claimed in claim 37, wherein said pharmaceutically acceptable salt of clopidogrel is prepared by exchanging with another salt.

41. The process as claimed in claim 39 or 40, wherein said pharmaceutically acceptable salt of clopidogrel is prepared in a solvent selected from the group consisting of of alcohol, ester, ether, ketone and acetonitrile or a mixture thereof.

42. The process as claimed in claim 41, wherein said alcohol when used as reaction solvent is selected from the group consisting of methanol, ethanol, n-propanol, isopropanol, n-butanol and t-butanol.

43. The process as claimed in claim 41, wherein said ketone when used as reaction solvent is acetone.

44. The process as claimed in claim 41, wherein said ester when used as reaction solvent is selected from ethyl acetate or butylacetate.

45. The process as claimed in claim 41, wherein said ether when used as reaction solvent is tetrahydrofuran.

46. The process as claimed in claim 22, wherein the solvent used for finally isolating clopidogrel or its salt is a ether selected from t-butyl methyl ether or di-isopropyl ether.

47. A novel salt of clopidogrel selected from the group :
clopidogrel mesylate (clopidogrel methane sulfonic acid salt), clopidogrel hydroiodide, clopidogrel besylate, clopidogrel oxalate, clopidogrel trifluoroacetate, clopidogrel acetate, clopidogrel nitrate, clopidogrel perchlorate, clopidogrel phosphonate, clopidogrel benzoate, clopidogrel fumarate, clopidogrel maleate, clopidogrel citrate, clopidogrel tartrate, clopidogrel benzene sulfonate, clopidogrel gentisate, clopidogrel pamoate, clopidogrel palmitate, clopidogrel succinate, clopidogrel estolate, clopidogrel acistrate, clopidogrel stearate, clopidogrel propionate, clopidogrel hippurate, clopidogrel salicylate, clopidogrel methylsulfate, clopidogrel tannate, clopidogrel lauryl sulfonate, clopidogrel lactate, clopidogrel glutamate, clopidogrel trichloroacetate, clopidogrel maleate, clopidogrel glutarate, clopidogrel N-acetyl-L-glutamate, clopidogrel sulfate and clopidogrel gluconate .

48. A novel salt of clopidogrel, as claimed in claim 47, wherein said salt is clopidogrel hydroiodide.

49. A novel salt of clopidogrel, as claimed in claim 47, wherein said salt is clopidogrel mesylate.

50. A novel salt of clopidogrel, as claimed in claim 47, wherein said salt is clopidogrel perchlorate.

51. A pharmaceutical composition comprising one or more clopidogrel salt(s) as defined in claim 47 as active ingredient(s) in association with a pharmaceutically acceptable solvent, diluent or excipient.

52. The pharmaceutical composition as claimed in claim 51, wherein the angle of repose of said active ingredient is in the range of 25 to 45^0

53. The pharmaceutical composition as claimed in claim 51, wherein said active ingredient has a better tapped density and solubility.

54. The pharmaceutical composition as claimed in claims 51, 52 or 53, wherein the pharmaceutically acceptable salt is clopidogrel hydroiodide.

55. The pharmaceutical composition as claimed in claim 51 in the form of tablets, coated tablets, capsules, injectables or suppositories.

56. Clopidogrel hydroiodide as claimed in claim 48, characterized by X-ray powder diffraction (XRPD) pattern with peaks at two-theta values at about : 3.7 ± 0.2, 4.3 ± 0.2, 5.2 ± 0.2, 8.7 ± 0.2, 9.6 ± 0.2, 11.4 ± 0.2, 12.8 ± 0.2, 13.8 ± 0.2, 16.6 ± 0.2, 17.0 ± 0.2, 17.7 ± 0.2, 18.0 ± 0.2, 18.8 ± 0.2, 19.2 ± 0.2, 20.6 ± 0.2 at degrees 2θ.

57. Clopidogrel hydroiodide as claimed in claim 48, characterized by X-ray powder diffraction (XRPD) pattern with peaks at two-theta values (Values in parentheses indicate the lattice spacing in angstroms) at about : 3.7 ± 0.2 (23.592), 4.3 ± 0.2(20.441), 5.2 ± 0.2(16.895), 8.7 ± 0.2(10.072), 9.6 ± 0.2(9.179), 11.4 ± 0.2(7.693), 12.8 ± 0.2(6.862), 13.8 ± 0.2(6.396), 16.6 ± 0.2(5.334), 17.0 ± 0.2(5.191), 17.7 ± 0.2(4.983), 18.0 ± 0.2(4.899), 18.8 ± 0.2(4.715), 19.2 ± 0.2(4.596), 20.6 ± 0.2(4.292) at degrees 2θ.

58. The pharmaceutical composition as claimed in claims 51, 52 or 53, wherein, the clopidogrel salt is optionally dissolved in an organic solvent.

59. The pharmaceutical composition as claimed in claim 58, wherein organic solvent is selected from alcohols, halogenated hydrocarbons and ketones.

60. The pharmaceutical composition as claimed in claim 59, wherein alcohol is selected from methanol, ethanol, n-propanol , isopropanol, n-butanol or tertiary butanol.

61. The pharmaceutical composition as claimed in claim 60, wherein, said alcohol is methanol.

62. The pharmaceutical composition as claimed in claim 59, wherein, said halogenated hydrocarbon is methylene chloride.

63. The pharmaceutical composition as claimed in claim 59, wherein, said ketone is acetone.

64. Use of a pharmaceutical composition for anti-platelet aggregatory activity using clopidogrel mesylate or clopidogrel hydroiodide as active ingredient.

65. A process for racemization of methyl (R)-(-)-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate substantially as herein described particularly with reference to the examples.

66. An improved process for the preparation of methyl (S)-(+)-alpha-(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)-acetate i.e. clopidogrel or its pharmaceutically acceptable salt substantially as herein described particularly with reference to the examples.

67. A pharmaceutical composition substantially as herein described particularly with reference to the examples.

INTERNATIONAL SEARCH REPORT

Int nal Application No
PCT/IB2004/000305

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07B55/00 C07B57/00 C07D495/04 A61K31/4365 A61P7/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07B C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, EMBASE, BIOSIS, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 02/059128 A (CADILA HEALTHCARE LTD ; LOHRAY BRAJ BHUSHAN (IN); PANDEY BIPIN (IN); L) 1 August 2002 (2002-08-01) cited in the application page 5, scheme 1; pages 12-13, bridging paragraph	1-67
Y	WO 00/27840 A (SANOFI SYNTHELABO ; BAI TIBORNE (HU); BAKONYI MARIA (HU); DOMBRADY ZSO) 18 May 2000 (2000-05-18) cited in the application page 12 - page 16; examples	1-67
Y	JERRY MARCH: "March's Advanced Organic Chemistry - 5th Edition" 2001, JOHN WILEY AND SONS, INC. , NEW YORK , XP002288613 page 770 - page 775	1-67

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 July 2004	05/08/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Frelon, D

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2004/000305

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 466 569 A (SANOFI SA) 15 January 1992 (1992-01-15) example 7 & US 4 847 265 A (BADORC ALAIN ET AL) 11 July 1989 (1989-07-11) cited in the application	1-67
A	EP 0 281 459 A (SANOFI SA) 7 September 1988 (1988-09-07) example 1	1-67
A	EP 0 420 706 A (SANOFI SA) 3 April 1991 (1991-04-03) example 10	1-67
A	EP 0 099 802 A (SANOFI SA) 1 February 1984 (1984-02-01) example 1	1-67

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2004/000305

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Claim 64 is so formulated that it may be also directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int nal Application No
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